File Smoking and Health

CURRENT DIGEST

of Scientific Papers Relating to Tobacco Use

(Compiled and Described for Informational Purposes Only for The Council for Tobacco Research—U.S.A. The Summaries Are Not Intended to be Complete Scientific Abstracts.)

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Mr Sandi Cobb
Mr Walter Jo
Wed. You like to get these as they come out. Monthly. Let me know.

1. HEART AND CIRCULATION

BURNS-COX, C.J., CHONG, Y.H. & GILLMAN, R., University of Malaya, Malaysia

"Risk factors and the absence of coronary heart disease in aborigines in West Malaysia." (British Heart Journal 34/9: 953-8, 1972)

"Coronary heart disease has never been found in Malaysian aborigines. We report the position regarding some of the risk factors usually associated with coronary heart disease in 73 adult aborigine men.

"They lived a physically active life on a diet largely of unrefined carbohydrate in the jungles of central West Malaysia. None was obese and blood pressures remained low at all ages. While the mean serum cholesterols were low, varying between 141 and 156 mg 100 ml at different ages, the mean fasting serum triglyceride levels of 135 to 164 mg 100 ml were comparable with those found in the West. This may have been due to their high carbohydrate intake.

"The mean packed cell volume, serum albumin, and erythrocyte transketolase activity were normal, indicating that they were likely to have been adequately nourished.

"Isolated aborigines living deep in the jungle had significantly lower serum lipids and higher gamma-globulin levels than those living at the fringe in contact with the rest of Malaysian society....

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"Most aborigines smoke many hours daily from childhood and make their cigarettes from locally grown sun-cured tobacco. A small quantity of this rough tobacco is rolled in a leaf and smoked slowly so that an ounce lasts many days. While chronic lung disease, presumably chronic bronchitis and emphysema, is common, carcinoma of the bronchus is exceedingly rare. It may well be that if coronary heart disease is not common in a population cigarette smoking alone is not important in its genesis."

KORSAN-BENGTSEN, K., WILHELMSEN, L. & TIBBLIN, G., University of Gothenburg, Sweden

"Blood coagulation and fibrinolysis in a random sample of 788 men 54-years-old. II. Relations of the variables to 'risk factors' for myocardial infarction." (Thrombosis et Diathesis Haemorrhagica 28/1: 99-108, August 31, 1972)

"In a population of 788 men 54 years of age plasma clotting times, factor II-VII-X activity, factor VIII, fibrinogen, fibrinolytic activity and plasminogen have been compared to anthropomorphic variables, blood lipids, blood sugar, blood pressure, heart rate, lung function and smoking.

"It was found by multiple regression analyses that fibrinogen, plasminogen and factor II-VII-X activity were correlated to serum cholesterol, and secondary to systolic blood pressure, heart rate and blood sugar.

"Independent of these correleations, fibrinogen, plasminogen and factor II-VII-X activity were also negatively correlated to FEV_1 and VC which are measures of lung function....

"There is a negative correlation between fibrinolytic activity and weight, subscapular and thorax skinfolds, chest and waist circumference indicating that obese subjects have a low fibrinolytic activity. There is also a negative correlation between fibrinolytic activity and serum triglycerides but this is insignificant when the effect of obesity is taken into account.

"Smokers had a higher fibrinogen level than nonsmokers and ex-smokers, but no other significant correlations were found (Table 9). Smokers have lower FEV_1 values. As there also is a correlation between FEV_1 and fibrinogen the sample was separated into four groups. Smokers and nonsmokers were thus divided in those with high and low FEV_1, respectively, according to Table X.

"The statistical evaluation was made with simultaneous t-test of the hypothesis that all four groups were equal. It was found that there was a significant difference between smokers and nonsmokers both in the group with high and the one with low FEV_1....

"When the present results are evaluated it has to be taken into consideration that many of the correlations are very weak and can explain only a small percentage of the variance. On the other hand the present series gives us an opportunity to discover correlations which in small and inhomogeneous groups are hidden by other influences. This series of men are randomly selected and are of the same age so that unknown effects of age etc. are kept under control....

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Table 9. Blood congulation-fibrinolysis and cigarette smoking.

	Non smokers n = 158	Ex-smokers n = 209	Smokers 1–14 cigarettes/ day n = 184	Smokers ≥ 15 cigarettes/ day n = 138
Recalcification time in silicone tubes, seconds	407 ± 98	408 ± 102	414 ± 103	391 ± 97
PTT in silicone tubes, seconds	207 ± 52	210 ± 44	213 ± 44	207 ± 47
PTT in glass tubes, seconds	60 ± 14	57 ± 13	56 ± 8	57 ± 8
Factor II-VII-X, %	94 ± 14	99 ± 59	94 ± 17	91 ± 17
Factor VIII, %	129 ± 58	128 ± 67	128 ± 61	122 ± 44
Fibrinogen, mg/100 ml	313 ± 83	320 ± 71	351 ± 73*	349 ± 71*
Fibrinolytic activity, mm²	131 ± 22	133 ± 23	132 ± 24	134 ± 19
Plasminogen, Units/ml	17.8 ± 3.2	18.7 ± 3.1	18.5 ± 3.2	18.6 ± 2.9

* When compared with ex-smokers and non-smokers, $P < 0.001$.

Table 10. Fibrinogen, mg/100 ml (mean and stand. dev.), in groups divided according to smoking habits and the variable $\frac{\text{observed } FEV_1 \times 100}{\text{predicted } FEV_1}$.

	Observed FEV_1 × 100 / Predicted FEV_1 ≥ 100	Observed FEV_1 × 100 / Predicted FEV_1 ≤ 100
All smokers	338.2 ± 68.4 n = 195	355.4 ± 72.8 n = 224
Non smokers and ex-smokers	311.0 ± 70.2 n = 218	324.3 ± 81.6 n = 144

"The increased fibrinogen level in smokers was first thought to be explained by their reduced lung function and increased frequency of bronchitis. The results of the analysis shown in Table 10 indicates that another mechanism is involved. An alternative hypothesis is that the increased adrenalin secretion in smokers causes an increased free fatty acid level which in turn stimulates the synthesis of fibrinogen as shown by Pilgeram and Pickart (1968). This would explain why the two other 'reactants' plasminogen and factor II-VII-X are not increased in smokers."

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THORSTEINSSON, S.B., HARDARSON, T. & SAMUELSSON, S., Iceland

"151 sjuklingur med kransaeoastiflu a lyflaeknisdeild Landspitalans 1966 - 1968." (151 patients with myocardial infarction in University Hospital, Iceland, 1966-1968) (Laeknabladid 57/6: 255-75, December 1971: authors' English summary)

"The present paper is a retrospective study of all patients admitted to the University Hospital of Iceland 1966-1968 with acute myocardial infarction. The patients were 151 and the episodes of infarction were 157. All the patients fullfilling the WHO criteria were included in the study.

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"The men were 119 and women 32....

"Smoking seemed to increase the risk of myocardial infarction. The average age at the time of infarction was 57.9 for smokers, 62.1 for ex-smokers and 69.2 for nonsmokers, compared with overall average of 62.9. The age difference of 11.3 years between smokers and nonsmokers is statistically significant. This may however possibly be explained by the fact that smoking is more common in the younger age groups, although no information is available about smoking habits of the older age groups."

MEADE, T.W. & CHAKRABARTI, R., Northwick Park Hospital, Middlesex, England

"Arterial-disease research: Observation or intervention?" (Lancet II: 913-16, October 28, 1972)

"Known 'risk factors' for ischemic heart-disease (I.H.D.) account for only a modest proportion of its incidence; in particular, dietary fat intake and blood-cholesterol levels explain less than is often claimed. Intervention studies are, with few exceptions, not at present likely to improve understanding of etiology or pathogenesis very substantially. The foreseeable chances of successful primary prevention on any major scale are slender, particularly by the modification of personal habits. There is a pressing need for prospective observational studies in which new risk factors are identified, particularly those likely to give a more direct measure of thrombotic tendency....

"There is little doubt that cigarette smoking is associated with the development of I.H.D., especially in men up to the age of 50 or 55. General indications are that giving up the habit reduces the risk of subsequent I.H.D. somewhat, though this effect is probably not pronounced in those who give it up at the ages at which they are especially likely to develop clinical I.H.D. However, the overriding importance of stopping smoking in the context of lung cancer raises the question of how much effort should be directed to determining very precisely the results of giving up the habit so far as other less strongly smoking-associated diseases are concerned."

OSTER, K.A., Connecticut

"Predisposition to atherosclerosis." (Letter: Journal of the American Medical Association 222/6: 704, November 6, 1972)

"I must admire the skill, versatility, and endurance of the members of the National Heart and Lung Institute (NHLI)-sponsored Framingham group in reshuffling and rearranging the fixed set of data provided by their 16-year study of 5,209 adults. Like gambits on a chessboard of statistical analysis, the fragmentary pieces of information are moved according to the rules of regressive equations, which become more complicated with time....

"It would seem that the Framingham chess game utilizes only some of the white or some of the black pieces. Parochial in their approach, they disregard the rest of the world. Furthermore, by preselecting the so-called risk factors and naming them interchangeably risk, probability, incidence, and now 'precursors,' they change the rules of the game. One may

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well ask what other cross influences played a role to either promote or prevent the even progress of CHD, eg, specific allergies, viral infections, developing malignant neoplasms, and others.

"The most damaging effect of the Framingham study, however, lies in the misapplication and abuse of its results. It may be that atherosclerotic lesions can be initiated in the various anatomical distributions of the arterial tree by the same or similar cause; but hypertension, excessive or moderate cigarette smoking, or moderately elevated serum cholesterol levels are definitely not the 'precursors,' since manifestations of atherosclerosis can be found in young people with none of these conditions. Therefore, an attack against one of the atherosclerotic diseases through risk factor modification, will probably not carry the 'bonus' of reduced incidence (with the exception, of course, of preventing CHA by successfully lowering elevated blood pressure)....

"The danger of these epidemiological studies is that they try to get much yield from little effort. It is time, in my opinion, that different approaches to the prevention of atherosclerosis are tried, especially by the NHLI, instead of juggling stale and insufficient data. Rather than seeking easy bonuses, let us try by new research concepts to find the environmental cause of this miserable disease, which maims and kills the young and promising individuals of our society."

2. LUNG CANCER

WEISS, W., BOUCOT, K.R., SEIDMAN, H. & CARNAHAN, W.J., Philadelphia

"Risk of lung cancer according to histologic type and cigarette dosage." (Journal of the American Medical Association 222/7: 799-801, November 13, 1972)

"The risk of developing various histologic types of bronchogenic carcinoma was determined in a ten-year prospective study of 6,136 older men in relation to smoking habits at the beginning of observation. No lung cancer developed in 830 nonsmokers. Among the 2,580 men who regularly smoked cigarettes only and who were current smokers on entry, the risk of lung cancer increased with increasing daily cigarette consumption. The cancers were typed according to a modification of the World Health Organization classification. Well-differentiated squamous-cell carcinoma, small-cell carcinoma, and adenocarcinoma showed a dose-response relationship to cigarette smoking, but poorly differentiated squamous-cell carcinoma did not....

"There was a distinct gradient in the risk of bronchogenic carcinoma in relation to the number of cigarettes smoked per day from a low of 0.9 per 1,000 man-years among men smoking less than ten cigarettes per day to a high of 4.0 for men smoking 20 cigarettes or more per day. Adjustment for age and race made the gradient steeper....

"Rates were adjusted for age at entry (45 to 54 years, 55 to 64, 65 to 76, and 75 and over) and race (white, nonwhite) by the indirect method. The set of standard age- and race-specific rates was taken as the rates for the total of the three smoking categories. No adjustment was made for duration of smoking because the three dose categories were similar in this respect....

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"Kreyberg's assumption of little or no causal relationship between cigarette smoking and adenocarcinoma is not justifiable. In our study there were no adenocarcinomas among men who never smoked regularly, and, though the number of cases was small, the 14 adenocarcinomas that developed among cigarette smokers seemed to be dose related."

BLUMER, W., JAUMANN, R. & REICH, T., Zurich, Switzerland

"Motorisierung - wichtigste Ursache fur Krebsentstehung?" (Motorization - a very important cause of carcinoma?) (Praxis 61/16: 514-18, April 18, 1972: partial translation)

"According to our own earlier studies the persons in our town living along the main road complained more frequently of headaches and other disturbances affecting their sense of well being and consequently took many more analgesic tablets than did those who lived in the outer parts of the town. Therefore, the possibility existed that the persons living along the main road smoked more in order to get rid of their unpleasant feelings and that they for this reason developed carcinomas more frequently. The traffic would then only be the indirect cause of the development of carcinoma. Actually, Gsell and other authors have called attention to the fact that there is more smoking in cities than in the country. However, according to our study the opposite conclusion is more probable, namely, that in smokers carcinoma is found more frequently because on the average they more frequently live in polluted air. The statistics which have shown a relationship between smoking and carcinoma refer only to pulmonary carcinoma. But it is precisely pulmonary carcinoma which did not occur especially frequently in the persons living along the main road. Moreover, among the persons who died from carcinoma there were as many women as men. These women without exception had not smoked, and the percentage of them who had lived along the main road was 6-fold greater than the percentage who had lived in the outer parts of the town."

"LEGIS FILIUS"

"How to die." (The Medical Journal of Australia 2/13: 734-5, September 23, 1972)

"There are worse ways of dying than from lung cancer, which is less obstreperous than most malignant tumors and often has a fairly short and predictable course.

"Three eminent physicians of my acquaintance had this experience, and remained civilized and sociable almost to the end. Another one, who was an inveterate smoker, would have had a less distressful quietus with this condition than he did with some neurological illness, not precisely diagnosed but very long lasting.

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"If providence ordained that all the human species died at 70 to 75 years with lung cancer, this would be a merciful dispensation in many ways -- especially since pneumonia, 'the old man's friend' as it used to be called, is now deprived of its rightful victims by the intervention of antibiotics. As it happens, most of those dying of lung cancer are over 65 anyway, though undoubtedly it can be a great tragedy in younger patients, especially those with children still at school....

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"I have stopped patients from smoking innumerable times when it was causing symptoms and affecting health -- e.g., in all cases of peptic ulcer, patients with arterial disease causing claudication, all patients before undergoing operation, and after operation too in many cases, if they have had a hernia, for example. Often they stop smoking permanently, which is a distinct advantage unless they become too fat.

"But if smoking is not causing manifest symptoms, I suggest it is the patient's own choice whether he cares to take the risk of remote effects such as lung cancer, etc. We can only state the facts as precisely as they are known, and then leave it to the free decision of the individual. Also, we must not descend to distortion or exaggeration. On October 29, 1971, the secretary of the Anti-Cancer Council declared in a letter to The Age that 'cigarettes are the cause of 90% of lung cancer'. What he meant was that 90% of victims are known smokers -- while 10% are nonsmokers. The statement as it stands is so fallacious as to be mildly astonishing from one who has had a scientific training....

"Couldn't we recognize that there is not the slightest possibility of eliminating tobacco from our lives? Then concentrate our scientific endeavors on devising a 'safe' cigarette from which nicotine, tar and carcinogens (if they can be identified) have been eliminated."

GRAY, N., Anti-Cancer Council of Victoria

"How to die." (Letter: The Medical Journal of Australia 2/17: 968, October 21, 1972)

"I think it a mite uncourageous for Legis Filius to make rude remarks about me while hiding behind a nom de plume. I also think it slightly improper for you to publish such remarks without a signature....

"I actually wrote the letter he describes. Legis Filius is wrong when he says I did not mean what I said, because I meant exactly what I said. Sir Richard Doll states that between 88% and 93% of cases of bronchial carcinoma in England can be attributed to smoking...

"We are all entitled to our own views as to whether smokers' disease are bigger, better and nicer than drinkers' diseases. No disease is nice if it carries off a breadwinner. Diseases also are not nice if they disable, and plenty of smokers are short of breath from bronchitis and emphysema....

"All of these problems seem sizeable to me, and I think we should do anything we can to reduce them. It is indeed a pity that people need to be deprived of tobacco when they have a disease which is due to it, which is Legis Filius' approach; but when we so deprive them, all we are doing is closing the door when the horse had bolted. Surely it is better to stop people smoking before they start. We all know that cigarettes are very difficult to give up, and we might wonder how many of the patients advised to do so by Legis Filius were actually successful. Perhaps he will [illegible] and will sign his name when he does so."

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"LEGIS FILIUS"

"How to die." (Letter: The Medical Journal of Australia 2/18: 1037, October 28, 197

"I am sorry that Dr. Nigel Gray finds me rude and lacking in courage. However, the only point in his letter which seems to needs discussion is whether his declaration that 'cigarettes are the cause of 90% of lung cancer' is a fair statement in a letter he wrote to the Press. He names Sir Richard Doll as his source, in a long article from which I hope the following excerpts may be quoted:

"1. 'Bronchial carcinoma is no more preventible [sic] in the full sense of the word than any other type of cancer and is unlikely to be so until we have a more complete understanding of the mechanism by which the disease is produced.'

"2. After discussing seven other agents 'capable of causing bronchial carcinoma', he comes to 'tobacco smoke', and finds that: 'It may be calculated that smoking is responsible for approximately 88% of all cases of bronchial carcinoma in male doctors between 35 and 84 years of age.' He does not give the calculations by which he arrives at this figure, but acknowledges that 'calculations of this sort are open to a number of objections', and he 'does not imply that smoking was the only factor responsible'.

"Whether these statements of Sir Richard Doll entitle Dr. Gray to proclaim that 'cigarettes are the cause of 90% of lung cancer' I leave your readers to judge. Will he acknowledge that 10% of cases of lung cancer do indeed occur among nonsmokers? Is he able to tell us how this compares with the proportion of nonsmokers in the adult population? I avoided using his name, and chose for myself a pseudonym (with your consent), in hopes that the matters I raised could be considered objectively, even philosophically, and at any rate without rancour."

3. OTHER RESPIRATORY CONDITIONS

WOOLCOCK, A.J., COLMAN, M.H. & BLACKBURN, C.R.B., University of Sydney, Australia

"Factors affecting normal values for ventilatory lung function." (American Review of Respiratory Disease 106/5: 692-709, November 1972)

"As part of an epidemiologic survey in New Guinea, forced vital capacity, one-second forced expiratory volume, subdivisions of lung volume, and peak expiratory flow were measured in a population living in the highlands and in a population living on the coast. The highland population had larger values than the coastal population for all measurements, but the difference was greater in females and children than in males. The ventilatory function of the New Guinea coastal population was similar to that of other non-European populations whereas that of the highland population was similar to that of populations of European descent. Ethnic variations in ventilatory lung function appear to be due to differences in the size of the lungs at full inspiration....

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"In 1962, Gaensler noted that the ventilatory capacity of smokers was invariably worse than that of nonsmokers, but in the present study this was

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not found to be so. In fact, the results were similar to those of Ferris and co-workers, who found ventilatory capacity of young male smokers to be equal or better than that of nonsmokers, although they had a more rapid deterioration with age. There was no statistical difference in the values between smokers and nonsmokers in men or in women. In the New Guinea highland population studied, mostly home grown tobacco in cigar form was smoked, and the quantity smoked by an individual subjects was almost impossible to assess. Equal numbers of women smoke, and, in many instances, they smoked more frequently than the men; yet smoking did not affect their ventilatory function. From the present evidence, at least in New Guineans, it seems reasonable to include symptomless smokers within the normal population from whom regression equations for prediction of lung function are being derived."

MILNE, J.S. & WILLIAMSON, J., Royal Victoria Hospital, Edinburgh

"The relationship of respiratory function tests to respiratory symptoms and smoking in older people." (Respiration 29/3: 206-13, 1972)

"The $FEV_{1.0}\%$ was calculated from $FEV_{1.0}$ and FVC measured in a random sample of older people in Edinburgh [215 men, 272 women]....

"The association between smoking and $FEV_{1.0}\%$ is shown in table II and III. The results in table II suggest that the proportion of persons with a ratio < 60 is higher in cigarette smokers and that this proportion is higher in persons who have smoked cigarettes longer. The trends which are obvious in men are present but less marked in women. 32.4% of men, who smoke or have smoked cigarettes only, have a ratio < 60 compared with 6.7% who never have smoked, 11.5% pipe smokers and 11.1% mixed smokers. The difference in the proportions of male cigarette smokers and men who have not smoked cigarettes, with ratios < 60, is significant ($\chi^2 5.13$, $p < 0.05$). 33% of men who have smoked cigarettes for 40 years or more have ratios < 60 compared with 7.4% of those who smoked for 20-39 years and 9.8% of those who never smoked cigarettes. The latter group includes men who smoke pipes only. In women the difference in the proportions with ratios < 60 who have smoked for ≥ 40 years and 20-39 years seems to disappear.

"The association between daily consumption of cigarette tobacco (as more or less than 15 g daily) and $FEV_{1.0}\%$ is shown in table III. Disregarding the amount of tobacco smoked daily significantly more men who have smoked cigarettes for 40 years or more have ratios < 60 compared with those who have smoked for less than 40 years ($p < 0.05$). However, in men who have smoked for 40 years or more the proportion with ratios < 60 does not differ significantly in the groups who have smoked less than 15 g or 15 g and more daily. No significant difference in the proportions with ratios < 60 is found in men smoking less than 15 g or 15 g and more daily either as present cigarette smokers or as past and present cigarette smokers combined. The product moment correlation coefficients between number of years as a smoker and $FEV_{1.0}\%$ are -0.23 for men and -0.17 for women. These correlations are small but significant ($p < 0.01$)."

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HUTTEMANN, U., OSWALD, P., LODE, H. & HUCKAUF, H., Berlin University

"Uber den Einfluss langjahrigen Zigarettenrauchens auf die Lungenfunktion jugendlicher Normalpersonen." (Lung function studies in young apparently healthy cigarette smokers versus nonsmokers) (Respiration 29/3: 270-87, 1972: authors' English abstract)

"Spirometric and plethysmographic measurements combined with investigations of lung PV-characteristics by means of esophageal catheters were carried out in both 20 young healthy smokers and 20 nonsmokers. The mean age of all probands was 29 years. The following results were obtained: (1) Spirometric data and airway resistance were normal in all subjects. Viscous work of breathing, however, was significantly elevated in cigarette smokers. (2) The static elastic recoil pressures of all subjects fell within the normal limits given by TURNER in 1968. (3) Significance of long-termed cigarette smoking was demonstrated by a rise of static compliance and a pronounced frequency dependence of dynamic compliance. Respiratory findings present in cigarette smokers are related to peripheral airway changes. In addition, smoke-specific lesions may be due to disturbances of alveolar surfactant."

VAN GANSE, W., DEPOORTER, A.M., MEHEUS, A., EYLENBOSCH, W., VANHOORNEEN, M., VUYLSTEEK, K., DE VREEZE, G. & RAVEEL, E., University of Ghent, Belgium

"Bijdrage van de pulmonaire diffusiecapaciteit (transferfactor van de long) in het kader van bevolkingsonderzoek naar CARA." (The role of the pulmonary diffusion capacity (transfer factor of the lung) in screening for CARA) (Nederlands Tijdschrift voor Geneeskunde 116/28: 1167-72, July 8, 1972: authors' English summary)

"In the course of an epidemiological search for CARA (chronic aspecific respiratory affection) in a Belgian occupational group, the pulmonary diffusion capacity (T1) in apnoea was measured in 139 men between the ages of 20 and 60 years. The average T1 value was higher in the group with normal spirographic values and without symptoms of CARA than in the group with normal spirographic values with CARA symptoms. In the group free from symptoms of CARA, the smoking habits showed a correlation with the T1: every cigarette per day corresponds to a decrease of the T1 by approx. 0.2 units.

"The prediction of the T1 on the basis of height and age -- with a view to the determination of so called normal values -- is more accurate when for the calculation of the regression use is made only of the values observed in persons who have never smoked."

MARTIN, R.R., ANTHONISEN, N.R. & ZUTTER, M., McGill University, Montreal, Canada

"Flow dependence of the intrapulmonary distribution of inspired boluses ^{133}Xe in smokers and nonsmokers." (Clinical Science 43/3: 319-29, September 1972)

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"1. Starting at 50% vital capacity, boluses of ^{133}Xe were inhaled either at very low or maximal flow rates, the inspiration terminating at total lung capacity (TLC). Flow-dependent changes in bolus distribution were

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examined by measuring regional radioactivity and computing regional time-constants, and also by recording alveolar plateaux during the subsequent vital capacity expiration. Regional residual volumes, as a fraction of regional total lung capacities, were also calculated. Three groups of subjects were studied: young nonsmokers, young cigarette smokers, and older nonsmokers [seven subjects in each group].

"2. All three groups gave similar results in terms of regional time-constants though there was less variation in the results for young nonsmokers.

"3. Regional residual volumes also gave similar results in all groups although again there was less variation in young nonsmokers. In young smokers, residual volumes in some regions depended on the flow rate used in their measurement, which indicated intraregional inhomogeneity of function.

"4. In young nonsmokers alveolar plateaux after slow and fast bolus inspirations differed little; this was not the case either in older subjects or in smokers. The increased flow-dependence of the alveolar plateau is analogous with the increased frequency-dependence of dynamic compliance and probably indicates obstruction of small peripheral airways."

FEUEREISL, R., KRZHIVANEK, I., REIL, I., KUBIK, A. & FELKEL, Kh., Research Institute for Tuberculosis and Diseases of Respiratory Organs, Prague

"Effect of smoking on the cardiopulmonary function." (Klinicheskaya Meditzina 50/7: 82-4, 1972: translation)

"We have studied 95 men, residents of the Klin region in Bohemia, aged between 50 and 60, whose roentgenograms of the lungs showed no change. Among the subjects there were 44 nonsmokers (Group I) and 51 smokers (Group II). In the Group II two men had smoked less than 100,000 cigarettes during their lifetime, five men between 100,000 and 200,000 cigarettes, 16 men between 200,000 and 300,000, seven men between 300,000 and 400,000, thirteen men between 400,000 and 500,000 and 8 men over 500,000. The study groups were uniform, the subjects being of approximately the same age, none of them suffering from obesity; the mean weight of the smokers, however, was statistically proved to be higher than that of non-smokers. Just as incontrovertibly it was established that more smokers had cough, expectoration, acute respiratory disorders of the upper air passages and shortness of breath under physical exertion than nonsmokers. Neither group included persons with the history of blood spitting or pneumonia....

"In conclusion we can confirm the data observed by other authors that smoking leads to a considerable impairment of cardio-pulmonary functions. Yet in some individual smokers this impairment is absent. Thus, 5 men out of 51, who during their lifetime had smoked from 292,000 to 584,000 cigarettes, showed no objective signs of chronic bronchitis, electro-cardiographic changes in the state of repose or under physical exertion nor any increase in the general pulmonary air flow resistance in the respiratory tract."

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4. PREGNANCY

GOLDSTEIN, H., National Children's Bureau, London
versus
YERUSHALMY, J., University of California, Berkeley

"Cigarette smoking and low-birth-weight babies." (American Journal of Obstetrics and Gynecology 114/4: 570-3, October 15, 1972)

GOLDSTEIN:

"In the January 15, 1972, issue of the JOURNAL, Professor Yerushalmy presented some interesting new findings on the association between cigarette smoking in pregnancy and the incidence of low birth weight....

"In addition to presenting his new findings Yerushalmy deals with the question of whether smoking in pregnancy is associated with increased perinatal death. He concludes that, '...infants of smoking mothers do not experience higher perinatal mortality rates than infants of non-smoking mothers.' This statement, however, is not supported by the available evidence. There are a number of places in the article where the evidence has been misinterpreted, and I shall deal with these in the order that they appear.

"First, there seems to be an error in the calculation of the probability that a study of 2,000 births would show a statistically significant difference (presumably at the 5 per cent level) between the mortality rates of babies born to smokers and nonsmokers, if an increased mortality rate as high as 35 per cent actually existed. Depending on the average mortality rate in the population being studied, this probability works out at between 0.15 and 0.30. So, out of 14 studies, the number expected to show a significant difference should be between 2.1 and 4.2. At least two of the studies referred to show significant differences, and thus there is no evidence to reject an increase of 35 per cent in mortality rate due to smoking.

"Second, of the five analyses from the four major studies quoted by Yerushalmy, two studies (Yerushalmy's of blacks and Butler and Alberman's) show large and significant differences between smokers and nonsmokers, and three studies do not -- hardly a basis for arguing that the evidence is really all in favor of no difference in mortality rates!...

"I have tried to show that the available evidence does not support either Yerushalmy's claim that maternal smoking is unrelated to perinatal death or his claim that it is the smoker rather than the smoking which is causative. In the present state of knowledge, we have little alternative but to work on the assumption that smoking is harmful, and it would be a pity if his paper were to cause any reduction in efforts to persuade mothers to give up smoking during pregnancy."

YERUSHALMY:

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"First, it is important to ascertain whether infants of smoking mothers suffer higher neonatal mortality rates than those of nonsmokers. In the paper, I gave a very definite negative answer to this question. This was based on a comprehensive review of the literature. Mr. Goldstein bases his affirmative answer basically on a single study in which he participated, namely, the

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British study of Butler and Alberman. There are 14 relatively small studies and 4 studies based on large samples in which the question of the perinatal mortality rate is discussed in connection with smoking during pregnancy.

"As to the smaller studies, I stated as follows: '...the probability that 7 of 14 studies, each of which was based on some 2,000 pregnancies, would miss a 35 per cent increase in mortality rate, if such an increase really existed, is very small....' I thought at the time that the proof of this statement was not very complicated and, therefore, did not provide it in the text. However, since Mr. Goldstein states that, '...there seems to be an error in the calculation of the probability....,' I am providing the familiar textbook solution....

"Direct computation yields the cumulative probability:

$$Pr(X \geq 7) = 0.00366.$$

"This means that the probability is 0.00366 (or 3.7 in 1,000) that, among 14 studies, 7 or more will show infant death rates of smoking mothers no greater than those of nonsmoking mothers. Since this probability is very small, the hypothesis that an increase in neonatal death in infants of smokers exists is rejected.

"As to the larger studies, Mr. Goldstein uses the results of our studies among the blacks as support for the findings of the studies in which he participated. He states, '... two studies (Yerushalmy's of blacks and Butler and Alberman's) show large and significant differences between smokers and nonsmokers....' (the underscoring of the word significant is mine). I don't know what test of significance Mr. Goldstein used on our data, but in this case it is not necessary for me to go into great detail. The total number of blacks in our study was some 3,300. In a previous paper, with which Mr. Goldstein is familiar since he wrote a letter about it to the editor of the American Journal of Epidemiology, the breakdown is given as 2,219 nonsmokers and 1,071 smokers. The respective neonatal mortality rates were 17.1 and 21.5 per thousand. A simple test would show that the probability that a difference as large as or larger than this could have occurred by chance is very great ($\chi^2 = 0.75$; $P > 0.30$).

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"We are, therefore, left with only a single large study showing an increase in the perinatal mortality rate of infants of smokers and 3 large studies which found no such difference. These are in addition to the 7 relatively smaller studies which found no difference. Mr. Goldstein did not mention that the only study which found the difference, namely, the one in which he participated, was retrospective. All the other three were prospective....

"Mr. Goldstein closes his letter with the pious statement that, '... it would be a pity if his paper were to cause any reduction in efforts to persuade mothers to give up smoking during pregnancy.' May I say that, on the contrary, it would be a pity to recommend a course of action based on conjectures, subjective notions, and easy explanations not supported by available data. The hard scientific data show conclusively that it is not reasonable to expect that giving up smoking will cause a rise in birth weight. It is important to consider also the possibility that 'efforts to persuade mothers to give up smoking during pregnancy' may result in emotional stress and feelings of guilt among mothers who may have tried to quit smoking and did not succeed."

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MURPHY, T., JOYCE, N. & WILSON-DAVIS, K., University College, Dublin

"Perinatal mortality study at the National Maternity Hospital Dublin, 1968-1969." (Journal of the Irish Medical Association 65/6: 125-9, March 18, 1972)

"Over a twelve month period 179 perinatal deaths at the National Maternity Hospital were investigated and a control was taken for each case. Information was collected on a number of variables for each group of mothers including socio-economic grouping, booking in the hospital, source of referral of patients and antenatal care. A number of indices were studied in an effort to assess the level of antenatal care including testing of rhesus factor, hemoglobin estimation and blood pressure recordings. It was found that the control group appeared to have had a better level of antenatal care than the perinatal death group....

"The smoking habits of the mothers were investigated by including a question on the average number of cigarettes, if any, smoked per day during the current pregnancy. While more of the mothers in the perinatal death group were regular smokers there was not a significant difference between them. Previous studies have shown an association between birth-weight and smoking, this effect was analyzed only in the control group as birth-weight and gestation are significantly associated. A significant difference was found between the nonsmoking and the smoking groups of mothers. The overall mean birth-weight of babies born to nonsmokers was 3360 Gms., and that of those born to smokers 3133 Gms."

DOMAGALA, J. & DOMAGALA, L., Poland

"Zachowanie sie sredniej wartosci ciezaru ciala noworodkow w latach 1960-1969 oraz waga noworodkow matak palacych." (Mean body weight of neonates in 1960-1969 and weight of neonates of smoking mothers) (Wiadomosci Lekarskie 25/11: 963-6, June 1, 1972: paraphrased abstract)

In view of the increasing secular trend for birth weights to rise, the authors undertook an analysis of the mean birth weights of the 8,161 infants born in their hospital in the years 1960 to 1969. Infants whose weight might have been reduced by maternal diseases complicating pregnancy were not taken into consideration. The results showed that the numbers of 'gigantic,' premature, and average-weight neonates remained at an almost identical level over this 10-year period, male infants being heavier at birth. In seeking the reason for this maintenance of the mean birth weight at a constant level, consideration was given to the possible effect of tobacco smoking among women. Analysis of the birth weights of the 855 children born in the year 1969 showed that 85 of their mothers (10%) were smokers and that the children of these mothers weighed approximately 300 g less at birth than those of non-smoking mothers. Although statistical analysis (Fischer's test and Student's t-test) revealed no significant difference between the mean birth weights of smoking and non-smoking mothers (3,060 g vs. 3,380 g) or between the mean weights of the mothers in the two groups (27.3 kg vs. 27.6 kg), the occurrence of premature births was statistically significantly more frequent in the group of smoking mothers (25% vs. 7.05%) Owing, however, to the relatively small proportion (10%) of smoking mothers in the material analyzed, the maintenance of the birth weight of infants at a constant level over the 10-year period studied cannot be accounted for on the basis of the smoking factor.

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5. OTHER SYSTEMIC CONDITIONS

KESSLER, I.I., Johns Hopkins University, Baltimore, Maryland

"Epidemiologic studies of Parkinson's Disease. III. A community-based survey." (American Journal of Epidemiology 96/4: 242-54, October 1972)

"Community-based samples of patients with and without Parkinson's disease in Baltimore from 1967 to 1969 were obtained through the establishment of a representative panel of 112 physicians....The significantly reduced frequency of this condition among Negroes, reported in an earlier hospital-based study, was again observed. The same held for the significantly decreased relative risk of Parkinson's disease among cigarette smokers. Previously noted relationships between parkinsonism and other diseases, such as arteriosclerosis and encephalitis, were verified....

TABLE 6

*Number of patients who ever smoked cigarettes**

Age (years)	Males		Females	
	Cases	Controls	Cases	Controls
<45	4 (66.7)	3 (75.0)	0	1 (100.0)
45-54	8 (72.7)	13 (81.3)	5 (45.5)	4 (50.0)
55-64	19 (51.4)	28 (75.7)	7 (23.3)	20 (54.1)
65-74	17 (42.5)	20 (50.1)	11 (25.6)	12 (29.3)
75+	8 (28.6)	11 (73.3)	3 (15.8)	2 (11.1)
Total: All ages†	56 (45.9)	84 (69.9)	26 (24.5)	39 (36.8)

* Percentages in parentheses.

† In males, χ^2 (1 d.f.) = 12.22, $p < .0011$. In females, χ^2 (1 d.f.) = 3.20, $p > .05$.

TABLE 7

Mean age at onset of neurologic symptoms reported by cases who ever smoked or never smoked cigarettes

Neurologic symptoms	Sex	Ever smoked	No. of cases	Mean age (years)	95% confidence interval* (years)
Tremor	Male	Yes	51	57.4	± 3.18
		No	66	60.0	± 2.98
	Female	Yes	24	57.1	± 5.08
		No	72	58.6	± 3.41
Rigidity	Male	Yes	33	56.2	± 3.98
		No	38	59.7	± 3.45
	Female	Yes	11	55.9	± 8.74
		No	45	60.0	± 4.25
Hypokinesia	Male	Yes	38	59.7	± 3.90
		No	42	62.4	± 3.78
	Female	Yes	10	66.0	± 7.10
		No	53	62.2	± 3.35
Facies	Male	Yes	19	58.7	± 5.84
		No	18	60.6	± 6.88
	Female	Yes	7	62.1	± 8.82
		No	20	59.2	± 5.37
Speech	Male	Yes	27	58.3	± 3.96
		No	36	62.2	± 4.86
	Female	Yes	12	61.7	± 7.33
		No	31	59.8	± 6.12

* Calculated as $t_{.05}S_{\bar{x}}$, where $t_{.05}$ is the appropriate value for the degrees of freedom involved and where $S_{\bar{x}}$ is the standard error about the mean.

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"The smoking characteristics of parkinsonians, previously reported for hospitalized cases, were observed anew in the community-based sample. Patients destined to develop Parkinson's disease appear less likely to become cigarette smokers. If they do smoke, they tend to smoke fewer cigarettes and over a shorter period of time. They also are less likely to inhale and more likely to stop smoking for any reason. There is some indication that the neurologic concomitants of parkinsonism tend to become manifest at an earlier age among smokers as compared with nonsmokers. However, the possible significance of the latter finding was confounded by the younger mean ages of the smokers relative to those of the nonsmokers of each sex in this investigation.

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"The proportions of male and female controls who smoked were nearly identical to those of the Baltimore general population sample who were initially interviewed by the Commission on Chronic Illness in 1953-1954 and reinterviewed in 1966-1967. Thus, it is extremely unlikely that the relationships observed in the community survey were due to the selection of a control sample who smoked excessively.

"A small but consistent deficit of neurologic symptoms was noted among male parkinsonians who smoked, but not among the corresponding females, in the hospital survey. These findings were reversed in the present study, suggesting either that smoking does not substantially affect the neuropathologic course of Parkinson's disease or that considerably larger sample sizes would be necessary to demonstrate the effects with consistency. The latter explanation probably applies to the somewhat inconsistent, findings on cigar and pipe smoking habits of parkinsonians as well."

HAENSZEL, W., KURIHARA, M., SEGI, M. & LEE, R.K.C., National Cancer Institute, Bethesda, Maryland

"Stomach cancer among Japanese in Hawaii." (Journal of the National Cancer Institute 49/4: 969-88, October 1972)

"Study of 220 Japanese stomach cancer patients and 440 hospital controls in Hawaii revealed that migrants (Issei) from prefectures with the highest stomach cancer risks in Japan continued to display an excess risk in Hawaii, but this effect did not persist among their Nisei offspring. Lower risks were suggested for Nisei, but not Issei adhering to Western-style diets. These nativity distinctions are consistent with other studies suggesting that early exposures are critical. Associations of stomach cancer with consumption of specific foods were noted....

"Issei males accounted for the significant excess risk among smokers, no difference on this score being evident for Nisei males. The meaning of this result is further clouded by the absence of a regular gradient in risk by amount of tobacco used, the secondary contrast of males smoking 20^{+} and $\leqq 20$ cigarettes daily being essentially negative. Curiously, these findings parallel those obtained from prospective studies conducted in the U.S. white population which have described risks about 40% higher for smokers, not accompanied by a gradient in risk with amount used. Two of the three studies conducted in Japan also suggested that male cigarette smokers have higher stomach cancer risks. Cigarette smoking, as it bears on the etiology of stomach cancer, is not a primary concern here and we note merely the compatibility of these data with other studies."

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BROWN, R.R., FRIEDELL, G.H. & LEKLEM, J.E., University of Wisconsin, Madison

"Tryptophan metabolism in patients with bladder cancer of occupational etiology." (American Industrial Hygiene Association Journal 33/4: 217-22, April 1972)

"Excretion of urinary tryptophan metabolites after a 2-gm load of L-tryptophan was measured in patients with occupational bladder cancer

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(due to exposure to aromatic amines), and in matched exposed and unexposed control subjects from the same factory. No significant differences were found in mean excretions of kynurenine, acetylkynurenine, hydroxykynurenine, kynurenic acid, xanthurenic acid, indican, anthranilic acid glucuronide, o-aminohippuric acid, or creatinine. Some individual subjects had slight elevations of metabolites so that 2 of 8 patients with bladder cancer present, and 2 of 10 with a diagnosis of bladder cancer but free of disease when studied, were classified as having abnormal tryptophan metabolism. In this regard, their tryptophan metabolism resembled that of male patients from Boston (15% abnormal) rather than that of male patients from Wisconsin (35% abnormal)....

"Although smoking is correlated with an elevated incidence of bladder cancer, the smoking history of the four groups studied was quite similar, so this is not a factor. Further, although Kerr et al. reported an effect of smoking on tryptophan metabolism, this was not confirmed, and the relationship between smoking and bladder cancer is probably not mediated through alterations of tryptophan metabolism in smokers."

JAVIER, F. & SALETA, C., Spain

"Clinica de los tumores vesicales." (Clinical observations on vesical tumors) (Archivos Espanoles de Urologia 25/2: 209-24, March-April 1972: authors' English summary plus partial translation)

"The authors studied the symptoms and signs which may lead us to the diagnosis of a vesical tumor, as well as the frequency with which these appear in accordance with studies carried out and published in world literature.

"The sign of hematuria and the cystitis syndrome are those which show the greatest numerical frequency in the clinical treatment of vesical tumors. Their appearance seems to be related to the different characteristics of the new-formation.

"100 tumor cases proceding from the statistics of the Urological Service of the Hospital of the 'La Paz' Health City were studied which had been selected at random....

"The authors come to the conclusion that the hematuria is closely related to the grade of malignancy and infiltration as well as to the morphology, and to a less extent, to the localization and size of the tumor. The age as well as the habit of smoking do not appear to have any influence on the appearance of a hematuria....

"The relationship between tobacco and the first symptom is neither instructive nor valuable. The higher incidence took place in those who smoked much, and less in nonsmokers, but this has no validity because the incidence in the group which smoked less than 10 cigarettes per day, was zero while in nonsmokers it was 24.4%."

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QURAISHY, M.S., Christian Medical College, Vellore, India

"Hypertensive retinopathy: A clinical study." (Annals of Ophthalmology 3/8: 872-5, August 1971)

"This study correlates hypertensive retinopathy and high blood pressure states. Observations are based on 125 cases with blood pressures of 160/100 mm Hg. Retinopathic changes were present in 24.8% of these cases. Maximum incidence of hypertensive retinopathy occurred in the 41-50 age group, and was found predominately in male patients. Other factors, such as family incidence, tobacco addiction, intraocular tension, and albuminuria, were considered....

"Four percent of the patients with hypertensive retinopathy used tobacco and 41.6% of the other patients did so. Use of tobacco, therefore, did not appear to affect the incidence of retinopathy."

MEHTA, F.S., SHROFF, B.C., GUPTA, P.C. & DAFTARY, D.K., Tata Institute, Bombay, India

"Oral leukoplakia in relation to tobacco habits. A ten-year follow-up study of Bombay policemen." (Oral Surgery, Oral Medicine and Oral Pathology 34/3: 426-33, September 1972)

"Results from the second follow-up of a group of persons (Bombay policemen) 10 years after the first examination and 5 years after the first follow-up are reported. Only one patient with leukoplakia, among 117 patients followed for 10 years, has been reported to have developed carcinoma. The 10-year incidence (1959 to 1969) of leukoplakia was found to be 2.9 per cent, and the 5-year incidence (1964 to 1969) was 1.8 per cent. The 5-year and 10-year incidences were the same in the low age groups, but the difference increased in the higher age groups. It was observed that almost all leukoplakic lesions in the chewing-habit group regressed, whereas most leukoplakic lesions which persisted for 10 years were in the smoking-habit group. Pan chewing remains the most prevalent form of tobacco habit, but the highest increase was observed among cigarette smokers."

HAMNER, J.E., National Institute of Dental Research, San Antonio, Texas

"Betel quid inducement of epithelial atypia in the buccal mucosa of baboons." (Cancer 30/4: 1001-5, October 1972)

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"Twelve baboons were divided into two groups: five received a basic betel quid (betel leaf, areca nut, and lime) inserted into a surgically created buccal mucosal pouch three times per week for 42 months; seven baboons had Maharashtran tobacco added to the basic quid. At the end of 12 months of treatment, five of seven baboons in the betel/tobacco group exhibited varying degrees of epithelial atypia; three of five animals in the betel group revealed atypia to a lesser degree. Histologic features of epithelial atypia included variance in nuclear size and shape, nuclear hyperchromatism, loss of cellular polarity, loss of cellular cohesion, and ballooning of cells. Ulcerative, hemorrhagic lesions occurred in the buccal mucosa of all animals after 30 months. Severe epithelial atypia was seen microscopically in one betel/tobacco animal after 34 months and developed in three of seven buccal pouches in the betel/tobacco group following only

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42 months of quid insertion. It is postulated that lime in the betel quid serves to condition the buccal mucosal tissue, thus rendering it susceptible to the weak carcinogenic effect of Indian tobacco, producing the marked epithelial atypical changes. Continued betel/tobacco treatment for a longer duration should lead to definite malignant invasion."

6. STATISTICS

FONTAINE, S.C., HENSCHKE, U.K., LEFFALL, L.D., Jr., MASON, C.H., REINHOLD, A.W., SCHNEIDER, R. & WHITE, J.E., Howard University College of Medicine, Washington, D.C.

"Comparison of the cancer deaths in the black and white U.S.A. population from 1949 to 1967." (Medical Annals of the District of Columbia 41/5: 293-8, May 1972)

"From 1949 until 1967 the number of deaths from all cancers increased twice as rapidly in the Black as in the White U.S. population (5.0% vs. 2.5% per year). The increase was much higher for Black males (7.1% vs. 3.1% per year) than for Black females (3.21% vs. 1.9% per year). About 7,000 fewer cancer deaths would have occurred in 1967 in U.S. Blacks if the increase in cancer deaths since 1949 had been the same as in U.S. Whites.

"Of the 24 most frequent U.S. cancers, 18 recorded a more rapid increase of the cancer deaths in Blacks than in Whites from 1949 to 1967. Three cancers, namely, stomach cancer, cervix cancer, and rectum cancer, remained essentially unchanged in Blacks, while they decreased significantly in Whites. Only lymphosarcoma combined with reticulum-cell sarcoma, Hodgkin's disease, and connective-tissue cancer showed no statistically significant differences in Blacks and Whites....

"A more detailed analysis of the magnitude and of the causes of this cancer gap is essential to find ways to stem the rapid rise of cancer deaths in the black U.S. population. Such a study would also give clues to the etiology, prevention and treatment of many cancers in all races....

"Without more detailed studies, one can only speculate at this time about the causes for the more rapid rise of cancer deaths in the black U.S. population. It seems obvious that there are a number of different causes, and that they contribute in different degrees to the increase of each individual cancer. The most important factors in our opinion are:

"Differences in exposure to carcinogens. For cancer of the lung, larynx and bladder one may suspect that in the last decades the number of black cigarette smokers has increased faster than the number of white cigarette smokers. For cancer of the esophagus, the pharynx, the tongue, the liver, and the pancreas an increasing exposure to alcohol must be considered as a possibility for the faster rise of those cancers in the black population. Other carcinogens in food and in the environment may also contribute significantly to the faster increase of cancer in U.S. Blacks."

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VAN DER LENDE, R. & ORIE, N.G.M., State University Hospital, Netherlands

"The MRC-ECCS questionnaire on respiratory symptoms. (Use in Epidemiology)." (Scandinavian Journal of Respiratory Diseases 53: 218-26, 1972)

"In epidemiology the basic principle is to compare groups of persons. For such studies, therefore, history taking with 'open' questions is unsuitable, certainly in investigating such a complicated disease as chronic non-specific lung disease (CNSLD). Use should be made of standardized questionnaires on respiratory symptoms, because only in this way may answers to the questions be compared.

"There are various types of questionnaires on respiratory symptoms, and the advantages and disadvantages of using them are discussed. In field studies on CNSLD, the questionnaire approved by a Committee of the British Medical Research Council (MRC) and the questionnaire of the European Community for Coal and Steel (ECCS) are very often used. Both questionnaires are comparable to each other as regards the questions on respiratory symptoms. It is, however, absolutely necessary that interviewers using the questionnaire be trained according to strict rules that are described in instruction booklets.

"If the questionnaires are applied properly, they prove to be a valid method of investigation in the epidemiology of CNSLD."

MILNE, J.S., MAULE, M.M., CORMACK, S. & WILLIAMSON, J., Western General Hospital, Edinburgh, Scotland

"The design and testing of a questionnaire and examination to assess physical and mental health in older people using a staff nurse as the observer." (Journal of Chronic Diseases 25/6 & 7: 385-405, July 1972)

"A questionnaire has been devised based on another study by the authors and on the publications of other workers to estimate physical and mental illness in older people. A simple physical examination follows the questionnaire. A staff nurse was trained to use the questionnaire and do the examination. Her performance was found to be satisfactory in respect of accuracy and reproducibility....

"Questions in the original study revealed 79 per cent of men and 26 per cent of women as smoking or having smoked cigarettes. As expected, cigarette smoking was associated with an increase in symptom prevalence when compared with nonsmoking. Pipe smoking did not have this association since only 7 per cent of 26 pipe smokers in the original study had persistent cough and phlegm compared with 38 per cent of 170 male cigarette smokers and 7 per cent of 17 male nonsmokers. The new questionnaire therefore asks about duration and amount of cigarette smoking only (Appendix A.4)."

[The appended questionnaire includes only three questions for current cigarette smokers, two for nonsmokers, five for former smokers.]

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7. TWIN STUDIES

CHERRY, W.H. & FORBES, W.F., University of Waterloo, Canada

"Smoking and health." (Letter: Lancet II: 824-5, October 14, 1972)

"Professor Burch calls for a worldwide twin study to distinguish between causal and constitutional factors in the association between cigarette smoking and disorders such as coronary heart-disease and lung cancer. This proposal is based on the results obtained by Friberg et al. for monozygotic and dizygotic twins, which suggest to Friberg and Burch that differences in mortality between populations of smokers and nonsmokers are a consequence of differences in genetic and other inherited factors.

"This interpretation of Friberg's results is open to several criticisms. First, the published data provide no direct information about differences in mortality within individual pairs of twins. That is, the data only provide information about deaths in two populations, each member of which happens to have a twin in the other population; it is not stated in how many instances both, one, or no twins in a pair have died. Hence, data permitting comparisons within twin pairs, where one twin serves as a control for the other (which represents the unique value of this type of experiment), are not available to the reader. For example, for monozygotic twins, where Friberg observes approximately equal numbers of deaths for nonsmokers and smokers (viz., 4 vs 5, and 4 vs 6 deaths, respectively, for males and females), it is possible that, on average, the smokers died at an earlier age....

"A worldwide twin study, as suggested by Professor Burch, would take a number of years to complete; and since, at present, there is little evidence that such a study would alter the main conclusions concerning the effects of cigarette smoking on health, a lower priority should be given to such a study than to research on reducing the accepted hazards."

HRUBEC, Z. & SUTTON, E.S., University of Texas, Austin

"Smoking and health." (Letter: Lancet II: 932, October 28, 1972)

"Relevant to Dr. Wakeham's suggestion is a study of morbidity carried out on the N.A.S.-N.R.C. twin panel which replicates the results of a study of morbidity carried out in Sweden. The study of the N.A.S.-N.R.C. twins is based on smoking information obtained by questionary in 1967. The panel consists of male twin pairs born in 1917-27. Due to their relatively young ages the twins responding to the questionary have not yet experienced sufficient mortality for a meaningful study to have been undertaken. However, as the twins age, such a study will soon become feasible.

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"Because of the rather small numbers of twin pairs with discordant smoking habits, it is important to consider the rigor and comparability of methodology of the Swedish, Danish, and U.S. studies, and other such studies that might be contemplated in the future elsewhere. The Committee on Epidemiology and Veterans Follow-up Studies of the National Research Council has recommended that an international group under independent auspices should be formed consisting of epidemiologists, statisticians, and experts in twin research that would consider these methodological problems.

"A suitable administrative framework to support such a group could be provided through the World Health Organization, or some other suitable

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FRIBERG, L., Karolinska Institute, Stockholm, Sweden

"Smoking and health." (Letter: Lancet II: 973, November 4, 1972)

"Dr. Cherry and Professor Forbes are sceptical of Professor Burch's proposal of worldwide twin studies. One reason given is that, at present, there is little evidence that such studies would alter the main conclusions concerning the effects of cigarette smoking on health. For certain pulmonary diseases (e.g., lung cancer) the causal relationship with cigarette smoking is quite clear. On the other hand, twin studies might well be of substantial value even for these effects -- for example, to find out whether certain persons are more susceptible than others to an effect of cigarette smoking. For other effects, including high mortality in general and particularly, for example, in coronary heart-disease, we feel that the case against cigarette smoking per se is not all that strong and in our opinion international collaboration using twins as target populations would be extremely useful. The problem in twin studies, even using a population the size of Sweden's, is to get enough numbers in different, well-defined smoking discordant groups. We are happy to learn that Dr. Cherry and Professor Forbes do not live up to their own objections to creating new registries. As can be seen in a recent paper of theirs, they state, 'A twin study is being planned, partly to investigate further the observations, on smoking discordant twins, reported by Friberg et al....'

"While large-scale twin studies until now have primarily focused on the health consequences of smoking, the twin method has a much broader applicability to a large number of medical and social problems concerned with the interrelationships between environmental agents and their impact upon the genetic constitution. The importance of these interrelationships was precisely the reason for a recent expansion of the Swedish twin registry in collaboration with the National Environment Protection Board to include an additional 15,000 pairs born from 1926 to 1942."

8. CANCER IMMUNOLOGY

RUCKDESCHEL, J.C., CODISH, S.D., STRANAHAN, A. & McKNEALLY, M.F., Albany Medical Center, New York

"Postoperative empyema improves survival in lung cancer. Documentation and analysis of a natural experiment." (The New England Journal of Medicine 287/20: 1013-17, November 16, 1972)

"A retrospective chart study revealed improved survival rates in patients in whom empyema developed after surgical resection for carcinoma of the lung. The overall five-year survival rate for the empyema group of 18 patients was 50 per cent, compared to an 18 per cent five-year survival rate in a control group consisting of a random 34-patient sample of resected cases at this institution. On further analysis, the beneficial effect of intrapleural infection was found principally in patients with tumor limited to the lung and its draining regional lymph nodes. Six of seven patients in this group survived for five years.

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"The protection from recurrent cancer conferred on these patients by postoperative empyema may have been mediated by the activation of regional cellular immune mechanisms. The reaction between immune lymphocytes and bacterial antigens is believed to release lymphokines and activate macrophages that nonspecifically destroy residual tumor cells while containing the intrapleural infection."

MOORE, G.E., Roswell Park Research Institute, Buffalo

"Iatrogenic immunotherapy of lung cancer." (Editorial: The New England Journal of Medicine 287/20: 1042-3, November 16, 1972)

"The study reported in this issue is interesting and supports similar reports but suffers from the inconsistencies that plague most retrospective clinical studies. Perhaps the surviving patients with empyema represent a select group; those with residual cancerous tissue may have been more susceptible to the infection and died within 30 days. No mention is made of empyema after the 30-day period; it is difficult to believe that it did not occur. A number of authors have reported approximately the same five-year survival in patients treated by lobectomy or pneumonectomy. It is strange, therefore, that in this study all the patients in the 'cured' empyema group had had pneumonectomies, whereas in the control patients, there were an equal number of long-term survivors after both procedures....

"But the heart (and lungs) of the matter is the nature of carcinolysis if it occurs. The authors have depreciated the role of a direct effect of the bacteria on tumor cells and have suggested that an immunologic reaction is most likely....

"Model experiments to test the thesis presented in this report would be difficult, but not impossible to design. Squamous carcinomas of the bronchi can be induced in rodents, and one could easily collect a mixed bag of organisms from most operating rooms. The use of a parallel experiment with germ-free animals should help to separate the effects of bacterial infection from those of immune reactions.

"It is humiliating that we have not been able to eliminate the health hazards of cigarette smoking and thus reverse the pandemic of lung cancer. Successful preventive measures would eliminate the desperate consideration of empyema as a curative adjunct to lung-cancer surgery."

PFEIFFER, E.H., Mainz University, West Germany

"Untersuchungen uber die Wirkung der Pockenvakzination auf die Entstehumg 3,4-Benzpyren-induzierter Tumoren." (Studies on the effect of small pox vaccination upon the development of 3,4-Benzo(a)pyrene-induced tumors) (Zentralblatt fur Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene 156/1: 115-128, 1972: author's English abstract)

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"The objective of our experiments with male NMRI mices was, to determine the influence of the small pox vaccination on the development and the periods of development of the 3,4-Benzo(a)pyrene-induced tumors as well as the time of survival of the tumor bearing animals. After a s.c. injection of 10 mg Benzo(a)pyrene which was suspended in polyethylene glycol

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diluted with physiological NaCl-solution an immunization with vaccinia virus was performed 8 days later.

1. Compared with the control group which had Bp applied only, the time progress of development of the tumor was different. A statistical analysis of the tumor rates per period during the experiment resulted in significant difference after the ending period of 10th, 12th and 14th week.

2. The average latent period of development of the tumor was reduced significantly by a one-time small pox vaccination.

3. A statistical analysis of the death rates which was made on the basis of the life table method in analyzing survival revealed a significant difference in the interval of the 16th and the 18th week.

4. A statistically significant difference could not be calculated at the average life time.

5. An effect on the total tumor rates could not be determined because of the very high doses of Benzo(a)pyrene application.

6. A two-time small pox vaccination revealed the same results as the one-time vaccination."

HANNA, M.G., Jr., TENNANT, R.W., YUHAS, J.M., CLAPP, N.K., BATZING, B.L. & SNODGRASS, M.J., Oak Ridge National Laboratory, Tennessee

"Autogenous immunity to endogenous RNA tumor virus antigens in mice with a low natural incidence of lymphoma." (Cancer Research 32: 2226-34, October 1972)

"The immune reactivity to endogenous (wild-type) RNA tumor virus-related antigen(s) was evaluated in RF mice, a strain with a low natural incidence of lymphoma. The purposes were to determine whether maintained humoral immunity could be detected and to evaluate the response with respect to the immune-mediated pathogenesis of glomerulo-sclerosis and incidence of tumors of lymphatic origin. Measurements of detectable murine leukemia virus antigen in the thymus and spleen were correlated with the development of immune competence, glomerulosclerosis, and the incidence of lymphoid neoplasia. Also, the specificity of the antibody that lodged in the kidney was determined by elution and indirect immunofluorescence with Gross virus-infected cells. A marked decrease in detectable murine leukemia virus antigen in thymus and spleen was found to correlate with development of immunological competence of the spleen as assayed by de novo germinal-center formation, antigen localization, and immune elimination from serum, which in turn correlated with occurrence of glomerulosclerosis. The antibody in the kidney was determined to be specific for Gross virus antigen(s). The role of this autogenous immunity may be considered to be beneficial in the RF mouse, as data correlating natural lymphoid neoplasia with severity of immune-complex glomerulosclerosis indicates that an inverse relationship is established in aged animals."

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Source: https://www.industrydocuments.ucsf.edu/docs/ytxk0000

TAN, E.M. & LERNER, R.A., Scripps Clinic and Research Foundation, La Jolla, California (CTR-grant)

"An immunological study of the fates of nuclear and nucleolar macromolecules during the cell cycle." (Journal of Molecular Biology 68: 107-14, 1972)

"Immunofluorescence employing specific antibodies was used to detect nuclear and nucleolar macromolecules during the cell cycle in synchronized diploid human lymphocytes. The majority of 'available' native DNA determinants were adjacent to the nuclear membrane in phase G_1. DNA associated with histones was present throughout the nucleus in phases G_1 and S and associated with chromosomes in metaphase. Single-stranded DNA was not detected in phase G_1 cells, but midway through phase S it was abundantly present. The morphology of the nucleolus changed markedly as cells proceeded from G_1 to metaphase, and in metaphase nucleolar fragmentation and the appearance of nucleolar contents in the cytoplasm were observed. Cytoplasmic DNA, which was not seen in G_1 or S-period cells, appeared adjacent to plasma membranes in metaphase cells.

"These studies demonstrated that specific antibodies against nuclear and nucleolar macromolecules could be important reagents for determination of the fates of certain macromolecules in eukaryotic cells."

9. PSYCHOLOGY

ABSE, D.W., WILKINS, M.M., KIRSCHNER, G., WESTON, D.L., BROWN, R.S. & BUXTON, W.D., University of Virginia Hospital, Charlottesville

"Self-frustration, nighttime smoking and lung cancer." (Psychosomatic Medicine 34/5: 395-404, September-October 1972)

"Two studies are described in which 65 lung disease patients were studied. Thirty-six of these patients had lung cancer; 29 had chest diseases other than lung cancer. Among the interview questions concerned with smoking behavior, the question of nighttime smoking aroused the greatest hesitation among patients. Sensitivity to this issue was found to be particularly great among lung cancer patients interviewed by a physician who did not smoke. In spite of this influence, however, cancer patients as a group did report more frequent nighttime smoking. It was also found that, while cancer patients had been smoking for a longer period of time and were smoking a greater amount, their nighttime smoking habits were not related to either of these variables. And finally, the observation that younger cancer patients smoke more frequently at night than do older cancer patients, suggested that the age of (cancer) onset may be significantly influenced by nighttime smoking habits.

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"We note that the smoking habits of lung cancer patients seem to occur within a very different psychophysiologic context than do the smoking habits of the general public. We are led to the conclusion, suggested by Eastwood and Trevelyan, that a classification of smoking patterns would be extremely useful. For example, it would be interesting to study cancerous and noncancerous smokers in terms of Russell's typology of smoking behaviors. On the basis of the present findings, we would expect lung cancer patients to evidence less psychosocial and indulgent smoking and perhaps more

Source: https://www.industrydocuments.ucsf.edu/docs/ytxk0000

tranquilization and addictive smoking. If so, such a finding would help us understand in what way the cancer patient's smoking habits differ and how these differences relate to his psychologic makeup....

"Given a possible link between nighttime smoking and increased susceptibility to lung cancer, it is necessary to understand why lung cancer patients so often smoke at night. The personality of the lung cancer patient, as depicted in the present study and in the general literature, suggests that these patients evidence a great deal of anxiety or depression, unrelieved through normal or neurotic channels of discharge. In fact, they score significantly lower on measures of neuroticism: they strive for independent self-expression and an avoidance of emotional and social involvements: and finally, they tend to report fewer psychosomatic complaints and greater stability in their marital lives.

"It is very interesting to compare these descriptions with those of smokers in general. Here, we find that smokers are a) impulsive, danger seeking and emotionally labile; b) more extroverted and more prone to psychosomatic disorders; and c) more often in the divorced or widowed category and more neurotic.

"These two descriptions, diametrically opposed, suggest that the psychologic characteristics associated with cigarette smoking clearly distinguish the lung cancer patient from the cancer-free smoker. Such characteristics, occurring within the context of progressively impaired emotional gratification, may contribute to the cancer patient's reported sleeplessness and tendency to smoke at night. Nighttime smoking, particularly during the later part of middle-age, may indicate an incipient though uncomplaining form of neurotic decompensation for several years prior to emergence of lung cancer symptoms....

"A further study, now being completed by the authors, contrasts cancer patients who smoke at night with a matched control group who also smoke at night. The former group is distinguished by evidence of poor interpersonal communication, inadequate sexual adjustment and conflicts involving both dependency and aggression. Thus it seems that for the cancer patient nighttime smoking is associated with a general impairment in emotional gratifications."

COBB, S., University of Michigan, Ann Arbor
versus
ABSE, D.W., WILKINS, M.M., BUXTON, W.D., BROWN, R.S., KIRSCHNER, G. & WESTON, D.L., University of Virginia

"Nighttime smoking and lung cancer." (Psychosomatic Medicine 34/5: 385-7, September-October 1972)

COBB:

"In this issue there is a paper by Abse and co-workers entitled Self-Frustration, Nighttime Smoking and Lung Cancer. This paper contains a curious interaction between astute clinical observation and an insensitivity to the meaning of numerical data. First, the authors are to be congratulated for presenting their data in sufficient detail to permit reanalysis....

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Source: https://www.industrydocuments.ucsf.edu/docs/ytxk0000

"The authors started with an hypothesis based on preexisting, well-supported clinical evidence that self-frustration of the need for stimulation is associated with lung cancer. They then postulate that nighttime smoking is the intervening variable. The hypothesis then goes as follows: self-frustration leads to nighttime smoking, and nighttime smoking increases the risk of lung cancer. In order to test the second part of this hypothesis, they have collected smoking histories on hospitalized patients with lung cancer and other lung diseases.

"When they started looking at their numbers, they found a significant bias in the data. It appears that those interviewed by smokers or interviewed in depth reported more nighttime smoking than those interviewed by nonsmokers. This they interpret as a response bias. However, improbable samples do arise by chance, and it is possible that by chance or by some vagary of the selection process the samples are simply different. If one assumes response bias, it is improper to combine samples. If one assumes sampling variation, one should combine the samples....

"At this point it is reasonable to conclude that the second part of the authors' hypothesis, that nighttime smoking is associated with increased risk of lung cancer, is supported for those who have smoked for less than 35 years. The sample is inadequate for concluding that such an effect does not occur among those who have smoked for 35 years or more; however, no evidence for a positive association was found in this long-smoking group. Perhaps nighttime smoking just does not add much to the risk of lung cancer for those who have already smoked so long.

"The authors started with evidence for the association of self-frustration with lung cancer. They have demonstrated an association of nighttime smoking and lung cancer. Then they adduced evidence from an as yet incomplete study that this self-frustration is associated with lung cancer independent of nighttime smoking. This is the only reasonable conclusion from a study of nighttime smokers with and without lung cancer that shows an association of self-frustration with lung cancer. We are now left with the probable conclusion that nighttime smoking and self-frustration may separately contribute to lung cancer.

"The authors are to be congratulated for having made an important contribution to our understanding of the relationship of smoking to lung cancer. It is to be hoped that they will further pursue the issue of self-frustration and lung cancer and further investigate the attractive, but so far unsupported, hypothesis that self-frustration contributes to lung cancer via nighttime smoking. Finally, an actual test of the hypothesis that cancer patients, but not other patients, are more willing to report their nighttime smoking to smokers rather than to nonsmokers, might lead to a further understanding of the problems of bias in self-report."

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ABSE et al:

"The approach which Cobb recommends, appears contrary to some basic principles of hypothesis testing. Without prior statistical justification, Cobb recombined our samples in a very selective fashion. His basis for selection -- ie, whether or not the patient had been smoking for 35 years, resulted in the exclusion of 74% of the cancer patients but only 11% of their controls. Such a drastic alteration of the original sample seriously affects the interpretation of results. Since duration of smoking is highly

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correlated with age (r = .70), Cobb effectively restricts the analysis to young cancer patients and their controls who also have a relatively short history of smoking. Which then is the relevant variable, age or smoking duration? Undoubtedly they both are. And to interpret all differences in terms of one is quite misleading. Cobb's statement 'perhaps nighttime smoking just doesn't add much to the risk of lung cancer for those who have already smoked so long' could just as easily be written '... for those who have already lived so long.' The increased risk of cancer with increasing age has been well documented and occurs irrespective of physical carcinogens, such as tobacco, or 'psychologic factors' such as extreme repression and self-frustration....

"Both duration of smoking and nighttime smoking are associated with the incidence of cancer -- ie, more lung cancer patients smoke at night and have been smoking for a longer time. Duration and nighttime smoking are independent, suggesting that whether or not one smokes at night is unrelated to the total number of years that he has been smoking. The interaction is not significant: that is, the association between nighttime smoking and lung cancer does not differ significantly for the two duration periods ($\leq$ 35 years and $>$35 years)....

"The above points illustrate several important statistical and methodological concepts. Of course, the most important issue here is that whatever 'hunches' or hindsights an investigator has, he cannot selectively resample the sample or change the original hypothesis, except within the confines of allowable statistical procedures."

SEGERS, M.J. & MERTENS, Ch., Catholic University of Louvain, Belgium

"Anxiete, depression et risque d'atherosclerose des coronaires." (Anxiety, depression and the risk of coronary atherosclerosis) (Acta Psychiatrica Belga 72/1: 46-55, January 1972: authors' English summary plus partial translation)

"The authors have tried to evaluate in 507 unselected subjects, the discriminative risk value of depression and anxiety scales, as well as bioclinical measurements in coronary atherosclerosis. Results show that psychological factors favor coronary atherosclerosis. They also show that there is no linear relationship between psychological and bioclinical parameters....

"The mean of depression is significantly higher in the category of subjects who smoke more than 25 cigarettes per day as compared with the categories of subjects who don't smoke at all, those that smoke, but less than 10 cigarettes, and those that smoke between 10 and 25 cigarettes per day. It seems very probable that depression, at a certain level, impells the subjects to make abusive use of tobacco."

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10. NICOTINE

MORRISON, C.F. & STEPHENSON, J.A., Tobacco Research Council Laboratories, Yorkshire, England

"The occurrence of tolerance to a central depressant effect of nicotine." (British Journal of Pharmacology 45: 151-56, September 1972)

"1. Rats were injected with 0.8 mg nicotine/kg, 0.8 mg amphetamine/kg or with saline immediately before being tested for 30 min in activity boxes.

2. During the first 3 trials the nicotine group were less active than the controls but from trial 5 onwards nicotine had a stimulant effect. The stimulant effect of the amphetamine did not alter with repeated injection....

"These experiments have demonstrated that rats developed a tolerance to the depressant effects of nicotine. This depended on the repeated administration of the drug and not on repeated experience of the experimental situation. Once the tolerance had developed it could, rather surprisingly, persist in the absence of further injections of nicotine. Nicotine has an initially depressant effect on barpressing behavior in the rat and this has been shown to be a central effect. It seems reasonable to assume that the depressant effect of nicotine on activity is also central, and the present results suggest a rapid adaptation to a central effect of nicotine. This may parallel the adaptation or development of tolerance to the unpleasant effects of smoking, such as nausea and sweating, experienced by the novice smoker....

"Nicotine has now been shown to increase, decrease or to have no effect on the activity scores of rats in activity boxes, depending on the animals' previous experience of nicotine. This could explain the apparent inconsistencies in the effects of nicotine on activity previously reported."

WEISS, G.B., Medical College of Virginia, Richmond

"On the site of action of nicotine in frog rectus abdominis muscle." (The Journal of Pharmacology and Experimental Therapeutics 183/1: 169-81, October 1972)

"Experiments were designed to elicit information about the cellular site of action of nicotine in frog rectus abdominis muscle. Nicotine (6.16 and 61.6 μM) increased muscle Ca retention after a subsequent 120-minute washout, decreased total Ca^{++} content and did not alter Ca loss when added during the slow component phase of the washout. Increasing pH from 6.80 to 9.40 increased nicotine-induced Ca retention and decreased the rate of development (but not the magnitude) of the contractile response. Procaine (3.67 mM), high K^+ (80 mM) and d-tubocurarine (25 μM) but not acetylcholine (ACh 2.3 μM) blocked contractions and increased Ca retention induced by nicotine, whereas nicotine blocked contractions elicited by ACh but not those obtained with high K^+. Hemicholinium-3 partially inhibited contractions and the increased Ca retention elicited by nicotine but did not affect similar actions of ACh. These results indicate that nicotine 1) acts at receptors at the neuromuscular junction and only a portion of these may be ACh receptors, 2) is active in both ionized and nonionized

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molecular forms and 3) does not exert these actions at sites beyond the neuromuscular junction. The varied responses obtained with either the ionized or nonionized forms of nicotine occur at similar extracellular concentrations. The importance of each of these stimulatory mechanisms in the evaluation of actions of nicotinic agents on frog rectus abdominis muscle is uncertain."

CRECELIU, V.H.-J. & FORWERG, W., Frankfurt on Main, West Germany

"Abscheidung von Nikotin-Aerosolen zur Bestimmung von Nikotin in Raumluft." (Separation of nicotine aerosols for the determination of nicotine in room air) (Zentralblatt fur Arbeitsmedizin und Arbeitsschutz 22/7: 200-3, July 1972: paraphrased English Abstract)

The authors had previously reported their development of a method for the measurement of nicotine in room air and in this report had described experiments showing that the method produced a quantitative (98%) separation of the nicotine vapor. However, a considerable proportion of the nicotine in cigar and cigarette smoke is present as a nicotine-containing aerosol, and in the present report the authors describe experiments to determine the degree of separation of the nicotine-containing aerosol obtained by this method. It was found that the mean degree of separation, using the same absorption solution as in the earlier studies (0.1 N sulfuric acid and 0.2% n-butanol), was at least 93%. The article contains diagrams and a detailed technical description of the apparatus used in this method.

11. SMOKE CONDENSATE AND CONSTITUENTS

HOFFMANN, D., RATHKAMP, G., NESNOW, S. & WYNDER, E.L., American Health Foundation, New York

"Fluoranthenes: Quantitative determination in cigarette smoke, formation by pyrolysis, and tumor-initiating activity." (Journal of the National Cancer Institute 49/4: 1165-75, October 1972)

"A method for the determination of fluoranthene in cigarette smoke was developed. The nonvolatile particulate matter of cigarette smoke was distributed between 2 solvent pairs, chromatographed on alumina, and the fluoranthene concentrate analyzed by gas chromatography, high-speed liquid chromatography, and paper chromatography. 9-^{14}C-phenanthrene and 9-^{14}C-benz[a]anthracene served as internal standards. The mainstream smoke of an 85-mm U.S. blended nonfilter cigarette contained 263 mg of fluoranthene, 116 ng of 1-, 3-, and 7-methylfluoranthene, 68 ng of 2- and 8-methylfluoranthene, and more than 100 ng of dimethylfluoranthenes. Pyrolysis experiments suggested that in cigarette smoke the fluoranthenes were partially formed via the Diels-Alder addition of acenaphthylenes with volatile dienes. Of the 5 possible monomethylfluoranthenes, 2- and 3-methylfluoranthenes were active as tumor initiators as were 2,3- and 7,8-dimethylfluoranthenes. 2-Methylfluoranthene was also active as a complete carcinogen....

"Although the initiating tumorigenicity of the active alkylfluoranthenes was significantly lower than that of BP, their higher total concentration in

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cigarette smoke (approximately 80 ng/cigarette) than BP (30 ng/cigarette) suggests, nevertheless, that they contributed somewhat to the overall tumor-initiating activity of cigarette smoke condensate. At present, the lack of data on the tumor-initiating activity of several other PAH in tobacco smoke permits no quantitative information as to the importance of the contribution of alkylfluoranthenes to the carcinogenicity of tobacco tar."

BHALLA, P.R., KOCHHAR, T.S. & SABHARWAL, P.S., University of Kentucky, Lexington

"Induction of mitotic abnormalities in the root tips of allium cepa by tobacco smoke." (Experientia 28/9: 1122-3, September 15, 1972)

"Nakanishi et al. while working with human epithelial lung cells treated with cigarette smoke condensate observed a decrease in average chromosome number to 76, from a modal value of 77 for the chromosomes in untreated cells. This finding was attributed to the appearance of dicentric chromosomes in some of the passages. Bouchard and May observed an increased number of mitotic abnormalities in mouse lung fragments that had been bathed for 24 h in a smoke condensate solution. Later investigations also found that cigarette smoke condensate has profound influence upon mammalian cells. Yet with a very few exceptions which are perhaps best exemplified by chronic granulocytic leukemia in humans, the observed chromosomal anomalies commonly found in cancer cells show no consistent pattern. The present investigation is another approach used to ascertain the feasibility of utilizing plant tissues as a quick and sensitive bioassay for tobacco smoke. Vacuolization of the cytoplasm, pycnotic nuclei and other mitotic abnormalities were seen 24 h after exposure to cigarette smoke. Other mitotic irregularities include occasional 'stickiness' of chromosomes at metaphase and bridging at anaphase and telophase. Thus, the present investigation clearly demonstrates that one can detect similar cytological responses in plants and animals exposed to tobacco smoke. A study of tobacco smoke and its constituents on plant tissues might lead to a better understanding of their mechanism of action. We are currently investigating the effect of different subfractions of tobacco smoke and results will be reported subsequently."

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ALEXANDROV, K. & FRAYSSINET, C., Villejuif, France

"The effect of cigarette-smoke condensate on the in vitro fixation of benzo(a)pyrene on DNA." (Experientia 28/8: 932-3, August 15, 1972)

"Bonds between the carcinogen B(a)P and the DNA molecule are possible in vitro with certain metabolites of carcinogen produced by aryl-hydroxylase located in the microsomes. In our experiments the cigarette smoke condensate is a very strong inducer of the hepatic microsomal enzymes.

"Comparable results have been reported showing that the inhalation of cigarette smoke is capable of greatly stimulating the enzymatic oxydation of B(a)P in the lungs of rats. Phenomena of a similar order have been demonstrated in the placenta of pregnant women who smoke.

Source: https://www.industrydocuments.ucsf.edu/docs/ytxk0000

"The smoke condensate when incubated with the microsomes is also capable of forming complexes with DNA. A second incubation of the DNA-condensate complexes with the metabolites of B(a)P-3H results in a much lower rate of fixation of B(a)P.

"The cigarette smoke condensate contains benzopyrene but in quantities too weak to cause a direct intervention: 1 mg of condensate that inhibits fixation in the order of 60% does not contain more than 0.04% of B(a)P added in the middle of the incubation.

"In addition, we must admit that in the cigarette smoke condensate there are substances different to B(a)P that can occupy the specific sites of fixation of this B(a)P on the DNA molecule."

GARCIA, H. & LIJINSKY, W., University of Nebraska

"Tumorigenicity of five cyclic nitrosamines in MRC rats." (Zeitschrift fur Krebsforschung 77/4: 257-61, 1972)

"Five cyclic nitrosamines have been fed to groups of 30 MRC rats at a concentration of 100 mg/liter in drinking water. Nitroso-3-pyrroline produced only tumors of the liver, and was the weakest carcinogen of the five. Nitrosopiperidine induced tumors of liver, esophagus and respiratory tract. Nitrosomorpholine induced tumors of liver and the nasal cavity. Nitrosoheptamethyleneimine induced squamous tumors of lung, and tumors of the esophagus and trachea and was the most potent carcinogen of the five. Dinitrosopiperazine induced tumors of the nasal cavity. The reasons for the pronounced organ specificities of these nitrosamines are discussed."

12. PREVENTIVE MEDICINE

[The journal, Preventive Medicine, August 1972, is a special "Forum Issue on Cancer." Many of the articles make passing reference to cigarette smoking. However, only the three given below were considered of sufficient interest to be abstracted.]

WYNDER, E.L. & MABUCHI, K., American Health Foundation, New York

"Etiological and preventive aspects of human cancer." (Preventive Medicine 1/3: 300-34, August 1972)

"There are only two ways to achieve the prevention of cancers associated with smoking: Do not smoke; manufacturs less tumorigenic tobacco products.

"The first means is clearly based on the individual decision. In order to provide a larger number of people with a motive to stop or not to start smoking, a continuing campaign to inform the public of the hazards of smoking is needed. The results of such a campaign are more likely to be fruitful if it is aimed at young people who have smoked only for a short while or who have not started smoking. In order to assist people who wish to stop smoking, the establishment of large numbers of smoking withdrawal clinics will be required. It is to be hoped that in the future every hospital will have an anti-smoking clinic as part of its health care facility.

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"In view of the accumulation of evidence indicating the value of developing less harmful cigarettes, the second means of prevention seems of special promise remembering that historically the great advances in preventive medicine were usually not based upon what an individual did for himself but rather what society did in terms of changing the product or the environment."

BELLOC, N.B. & BRESLOW, L., California State Department of Health, Berkeley

"Relationship of physical health status and health practices." (Preventive Medicine 1/3: 409-21, August 1972)

"This paper examines the relation between common health practices, including hours of sleep, regularity of meals, physical activity, smoking and drinking, and physical health status. Good practices are shown to be associated with positive health, and the relationship of these activities was cumulative; those who followed all of the good practices being in better health, even though older, than those who failed to do so. This association was found to be independent of age, sex, and economic status....

"In view of the extensive evidence on the relation between smoking and health, it is not surprising to find in Table 5 that those who had never smoked enjoyed better physical health than present or past smokers. The differences in physical health status, as measured by the PHR, relative to cigarette smoking are not as large as in the case of some other health practices. Men who had never smoked scored .47 compared with .51 for present and past smokers. Whether one inhales cigarette smoke and the extent of such inhalation appears highly correlated with physical health status."

WEBER, K.H., Hamburg, Germany

"Tar and nicotine in German cigarettes." (Preventive Medicine 1/3: 446-50, August 1972)

"During the past 15 years systematic measures of the German cigarette industry and a remarkable change in smoking habits in the Federal Republic of Germany have considerably reduced the per capita exposure to cigarette smoke. To achieve this goal, manufacturers have combined careful tobacco selection and the early introduction of filter cigarettes with several important technological improvements such as the continuous modification of cigarette filters, the finer cut of cigarette tobaccos, the improvement of paper porosity and the increasing use of homogenized tobacco leaf. Smokers have not only accepted these gradual changes, they have promoted this development by changing their smoking habits, e.g., smoking cigarettes down to longer butt lengths....

"1. Although cigarette consumption has increased by 37% it can be shown that the total intake of smoke condensate and nicotine per capita and per smoker has decreased by as much as 27% (condensate) and 20% (nicotine) in the Federal Republic of Germany between 1961 and 1970.

"2. During the last ten years a smoker who has not increased his daily consumption and who has followed the general tendency towards leaving long butts has, on the average, decreased his intake of condensate and nicotine by as much as 40%.

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"3. While per capita cigarette consumption has increased during the last ten years, there has been a marked reduction in the consumption of cigarette smoke.

"Very surprisingly, few studies about such developments have been published. Therefore, it seems highly desirable to collect more data of this type and use such information as a base for future research concerning the epidemiology of smoking and health."

REED, C.S., Sydney Hospital, Australia

"Are multiphasic health screening programmes a desirable innovation?" (The Medical Journal of Australia 2: 1018-24, October 28, 1972)

"The preventative aspects of coronary artery disease are looked into by clinical estimations of blood pressure, blood sugar levels, serum uric acid levels and serum cholesterol levels. Despite the known need for further projected data in heart disease detection (and it is claimed that these records will be useful for prospective studies), there has only been discussion of providing estimations of serum levels of triglycerides and lipoprotein electrophoreses, without which no competent physician feels at ease.

"Thus Ancel Key's study (1970) of 'Coronary Heart Disease is Seven Countries' made it clear that the so-called risk factors cannot explain differences in coronary heart disease in different countries. The so-called 'risk factors' include: (i) cigarette smoking; (ii) occupational and physical activity; (iii) body fatness and weight.

"There is a tendency for blood pressure and coronary heart disease to be linked, and overall the strongest relationships concern the percentage of men with serum cholesterol values over 250 mg/100 ml and the amount of dietary saturated fatty acids.

"However, despite this, Cochrane's (1970) ten-year study in the United Kingdom shows that serum cholesterol level, body weight or cigarette smoking does not correlate with mortality; only blood pressure shows his correlation."

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13. OPINIONS

JOHNSTON, L., United Kingdom

"Craving for tobacco." (Letter: Lancet II: 981, November 4, 1972)

"As an explanation of the operation of the craving for tobacco the vicious circle hypothesis, smoking⇆craving, though commendably concise, does not take account of all the facts.

"When a confirmed smoker stops smoking, what produces the unpleasant sensation, craving, is not, I think, known. It may be assumed, however, that whatever it is -- Let us call it C -- is produced by repeated smoking -- i.e., repeated doses of nicotine -- and that it is stored, probably, in the central nervous system. Soon after a smoke, the release of C from the store

Source: https://www.industrydocuments.ucsf.edu/docs/ytxk0000

commences, and when enough has been released to produce a certain level of craving, the smoker smokes again. If, however, he stops smoking, C continues to be released and to punish the smoker until either he re-starts smoking, or until the store of C, accumulated usually over years, runs out."

SOMMER, R.M., Redondo Beach, California

"Nonspecification of tobacco smokers." (Letter: Journal of the American Medical Association 222/4: 487, October 23, 1972)

"In the July 31 issue of The Journal, Dr. Daniell discussed the relationship between osteoporosis and smoking. The letter appeared to be well documented and convincing, but the theory is far from flawless. I am an ex-smoker and, like Dr. Daniell, am always searching to connect disease processes with the deleterious effects of smoking.

"Nevertheless, smokers and nonsmokers are different people, so they cannot be used as comparable study groups. Those who do not smoke for reasons of healthy living habits, also carry these living habits into sports activities, proper diet, etc, all of which contribute to a positive calcium balance and less osteoporosis. Furthermore, heavy smokers as a group do not force themselves to do regular exercise to a like extent, and are less likely to be capable of equivalent physical exertion, due to a higher incidence of cardiovascular and respiratory disease in this smoking group."

RAZANSKI, J.J., New York

"Osteoporosis and smoking." (Letter: Journal of the American Medical Association 222/7: 838, November 13, 1972)

"I wish to respond to Dr. Daniell's letter published in the July 31, 1972, issue of The Journal regarding the relationship between osteoporosis and smoking....As is well known, severe immobility can lead to osteoporosis. Decreased osteoblastic and increased osteoclastic activity occurs as a result of immobilization and lack of proper mechanical stress on bones. In Dr. Daniell's study, the group with idiopathic pre-senile osteoporosis included many subjects with severe chronic respiratory illnesses. Two of the patients died subsequently of chronic obstructive pulmonary disease. Thus, in this study, heavy smoking seems as likely to be related to osteoporosis via severe respiratory illness causing immobility as via the other mechanisms proposed to explain the findings.

"In rehabilitation medicine, severely immobilized patients are prevented from developing osteoporosis by tilt table therapy that gradually places proper mechanical stresses on the skeleton. Perhaps such treatment would be of benefit for certain patients with severe immobilizing respiratory diseases."

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14. BRIEFS FROM MEETINGS

American Heart Association, Dallas, November 16-19, 1972

The following numbered abstracts appeared in Circulation 46/4: October 1972, Supplement II.

GARCIA-PALMIERI, M., COSTAS, R., GORDON, T., KAGAN, A., KANNEL, W.B. & SCHIFFMAN, J., Puerto Rico Heart Health Program, San Juan

"Differences in coronary heart disease in Honolulu, Puerto Rico and Framingham." (375)

"Carefully standardized objective evidence of the prevalence and incidence of coronary heart disease (CHD) is now available for representative populations of men 45-64 in Framingham, Puerto Rico and among Honolulu Japanese. The prevalence of electrocardiographic evidence of myocardial infarction (MY by ECG) and the incidence of CHD (MI by ECG plus CHD death) in Puerto Rico and in Honolulu Japanese is half that in Framingham. A large number of population characteristics were compared. While serum cholesterol levels and amount of cigarette smoking are lower in Puerto Rico and Honolulu than Framingham, and blood pressure levels are nearly the same, these facts (individually or in combination) do not account for all the differences in CHD incidence or prevalence. These unexplained differences suggest the need for extending research to new areas than usual risk factors."

SPAIN, D.M., SIEGEL, H. & BRADESS, V., Brookdale Hospital Medical Center, New York

"Smoking habits and sudden death from coronary disease in women." (376)

"Smoking habits and sudden and unexpected death (S.D.) as the initial clinical event in coronary disease was studied in 181 medical examiner autopsied cases in women. 46% (84) were nonsmokers (N.S.), 20% (36) were light smokers (L.S.), and 34% (61) were heavy smokers (H.S.). Of the 29 S.D. from coronary disease, there were 10% (3) N.S., 28% (8) L.S., and 62% (18) H.S. The mean ages for this latter group were 67, 55, and 48 respectively. The male to female ratios of coronary S.D. as related to smoking habits in the N.S. were 11-1 (32-3), in the L.S. 4-1 (31-8) and in the H.S. 3.5-1 (62-18). Comparing the male to female ratios of coronary S.D. in those less than age 51 revealed a ratio of 12-1 (183-15) during 1949-1959, and a ratio of 5-1 (55-11) during 1967-1971. The close association of H.S. with coronary S.D. in young women, the markedly lower mean age at which this occurs, and the relative increase in the coronary S.D. in women as compared to men in the recent period which corresponds the increase in H.S. among women, strongly support H.S. as an important risk factor in S.D. from coronary disease."

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NOBREGA, F.T., OXMAN, H.A., CONNOLLY, D.C., ELVEBACK, L.R., TITUS, J.L. & KURLAND, L.T., Mayo Clinic, Rochester, Minnesota

"The high risk patients with angina pectoris." (378)

"With the increasing availability of diagnostic and therapeutic measures for patients with clinical ischemic heart disease (IHD), it has become important to identify patients at highest risk for cardiac death (CD) and subsequent myocardial infarction (MI) who might benefit most from the use of these measures. As part of a study of IHD among residents of Rochester, Minnesota, the medical records of all residents who had classical angina pectoris (CAP) as their initial manifestation of IHD were reviewed for the presence of prior risk factors. By means of stepwise discriminant analysis it was possible to determine that the most important factors for CD were: (1) cardiac enlargement by chest x-ray (2) diastolic hypertension (3) cigarette smoking (4) an abnormal resting electrocardiogram at the time of diagnosis of CAP and (5) an elevated cholesterol level. Using these variables and CD as the endpoint, we were able to correctly classify 92% as living and 75% as dead at five years. With these same variables, we were also able to accurately classify which patients were at highest risk for developing a MI within five years after the initial diagnosis of CAP. Using combinations of these variables we have been able to develop a risk profile for patients with CAP. Until the efficacy of the new surgical procedure is firmly established, these high risk factors should be considered in the selection of angina patients for early diagnostic and therapeutic intervention."

AHMED, S.S., MOSCHOS, C.B. & REGAN, T.J., New Jersey Medical School, Newark

"Cardiovascular effects of chronic smoking in beagles." (409)

"Chronic tobacco smoking has been associated with circulatory disorders, but the response separated from other risk factors has not been characterized. One year old litter mate beagles after permanent tracheostomy, were divided into seven controls, nine smoking 7 cigarettes/day and six receiving nicotine, 840 μg/kg i.m. After nearly two years the animals were catheterized under anesthesia for assessment of left ventricular function and volumes (indicator dilution). While heart rate, stroke volume, LV end-diastolic pressure and volume did not differ significantly in three groups, smokers had high systolic (153$\pm$ 6.6 vs 122$\pm$7 mm. Hg $P<0.01$) and diastolic pressures (109$\pm$4 vs 76$\pm$3.7, $P<0.001$). Diminished contractility was manifested by a reduced ejection fraction of 34.7$\pm$3 (vs 44$\pm$2.6% in normals, $P<0.005$) and the Frank-Levinson index of 1.41$\pm$0.12 (2.41$\pm$0.2 in normals, $P<0.05$). Reduction of arterial pressure to normal with hemorrhage did not alter these indices suggesting independence of afterload. Nicotine animals behaved similar to smokers, with markedly elevated peripheral resistance. Thus, both the arterial system and myocardium are affected at a level proportionate to cigarette usage in man."

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Source: https://www.industrydocuments.ucsf.edu/docs/ytxk0000

MANDEL, W.J., LAKS, M.M., HAYAKAWA, H. & McCULLEN, A., Cedars-Sinai Medical Center, Los Angeles

"Alterations of the hemodynamic effects of nicotine by autonomic blockade in the conscious dog." (746)

"Previous investigations using in vitro preparations or anesthetized partially intact animals demonstrated the complex cardiovascular effects of N. The purpose of this study was to define more clearly the effects of N in a preparation resembling the normal physiological state. In the conscious dog, N 10-600µg was injected into the right atrium (RA), during continuous right ventricular (RV), pulmonary artery (PA) and aortic (A) pressure monitoring. At 400µg, a triphasic response occurred: 1) 2-4 sec sinus arrest followed by bradycardia 2) subsequent sinus tachycardia and marked increase in A, RV systolic and diastolic pressure 3) subsequent bradycardia and gradual return to control pressures. However, RVedp remained elevated for 10-30 min. Arterial injections of 10-600µg, demonstrated: 1) No sinus arrest 2) more pronounced pressure elevations at lower dosage 3) secondary bradycardia. Atropine (0.025mg/Kg IV) eliminated the sinus arrest following RA injection. Propranolol (1.0mg/-Kg IV) diminished the secondary cardioacceleration and slightly diminished the pressure responses. It is concluded that, in the conscious dog, N: 1) a) releases acetylcholine in the RA, b) may depress myocardial function 2) subsequently releases catecholamines 3) lastly produces a reflex bradycardia."

PAFFENBARGER, R.S., Jr. & WING, A.L., California Department of Public Health, Berkeley

"High-risk factors common to coronary heart disease and adult-onset diabetes mellitus." (797)

"Of 27,000 college alumni from Harvard and the University of Pennsylvania who responded to mail questionnaires, 852 reported doctor-diagnosed coronary heart diseases (CHD) and 362 doctor-diagnosed adult-onset diabetes mellitus (DM), while 33 reported both diseases, 16-52 years after college entrance. Validation procedures suggested these findings were within acceptable limits. Student physical and social records identified high-risk factors of CHD and DM common to both and suggesting similarities in their etiologies. Age at college case-taking and interval of followup were held constant in computing incidence rates of CHD and DM to identify high-risk factors. Chief among factors associated with increased risk of CHD were 1) cigarette smoking, 2) higher levels of systolic and diastolic blood pressure, 3) physical inactivity, 4) heavier weight for height, 5) shorter body stature, 6) sense of exhaustion, and 7) early parental death. These factors also were associated with increase risk of DM except 1) cigarette smoking, 2) diastolic blood pressure, 3) physical inactivity, and 4) body stature. On the other hand, reduced vital capacity and dyspnea on exertion were forerunners of DM but not of CHD. Similarities and differences in high-risk factors of CHD and DM may identify appropriate avenues of intervention for each disease."

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Source: https://www.industrydocuments.ucsf.edu/docs/ytxk0000

RILEY, C.P., OBERMAN, A. & JONES, W.B., University of Alabama

"Angina pectoris in women." (837)

"Epidemiologic studies of coronary heart disease have shown a better life-expectancy for women than men with angina pectoris (AP). This study examines the diagnosis of typical, exertional AP, relieved by rest or nitroglycerin within five minutes, in patients having coronary arteriography (CAG). Coronary lumen stenosis of $\geq$ 50% in any vessel was considered an abnormal CAG. Of 134 patients with AP and CAG, 109 were men and 25 were women. A significantly higher rate of normal CAG was found in women (32%) than men (13%) ($p < .05$). No significant differences were found between women with AP and a normal CAG or an abnormal CAG for the following factors: age, systolic and diastolic blood pressures, smoking habits, serum cholesterol and triglyceride, and body weight.

"Normal CAG does not exclude a cardiac origin for AP; however, the presence or absence of major coronary lesions seriously affects prognosis. Although the number of patients studied is small, women with coronary artery disease have fared no better than men during a two-year follow-up period. The better life-expectancy of women than men with AP in epidemiologic studies may result from inclusion of many women without major coronary lesions."

SCOTT, R.A., HENSON, D.E., LESAK, A.E. & HASS, G.M., St. Luke's Medical Center, Chicago

"Relations between plasma free fatty acids and occurrence of calcific arteriosclerotic thromboarteritis in rabbits." (864)

"A regimen involving simultaneous use of nicotine, vitamin D and dietary cholesterol in rabbits resulted in a high incidence of peripheral calcific arteriosclerosis often complicated by thrombosis. Among 48 animals there was a positive correlation between the magnitude of nicotine-induced rise in plasma FFA and development of arterial disease. Calcific arteriosclerosis with thrombosis occurred in those (27) in which the rise exceeded 100%. Calcific arteriosclerosis without thrombosis occurred in those (13) in which the rise was about 50%. No arterial disease occurred in those (8) in which nicotine induced no rise in plasma FFA. When adrenalin was substituted for nicotine the rise in plasma FFA resembled that due to nicotine but only 4 of 15 developed arterial calcification. When nicotine was replaced by ACTH or heparin the rise in plasma FFA greatly exceeded that caused by nicotine and no animals developed arteriosclerosis or thrombosis. Hence the magnitude of rise in plasma FFA, as such, had no pathogenetic role in induction of peripheral arteriosclerotic thrombosis."

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SELTZER, C.C., Harvard School of Public Health, Boston

"Does it help to stop smoking?" (867)

"It is the present conventional wisdom that a decrease in cigarette smoking will result in a substantial decline in population death rates. It is based essentially on the oftentimes intermediate position of the death

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rates of ex-smokers relative to those of continuing cigarette smokers and nonsmokers. However, such a conclusion ignores the fact that ex-smoker data often give contradictory and inconsistent findings and pose a virtually insoluble problem as to valid interpretations that may be drawn from such data in the present study design. Apart from ex-smoker data, cohort data in which there has been a substantial decrease in cigarette smoking over time present a more direct opportunity to view possible changes in death rates. Just such data are available from Doll and Hill's British doctors study which shows about a 50% decline in doctors smoking cigarettes from 1951 to 1966. Yet, over the same period, there is essentially no change in the death rates of these same British doctors. The absence of correspondence between the death rates among British doctors from 1951 to 1966 and their simultaneous downward trend in cigarette smoking, is strong refutation of the claim by the Public Health Service and others in medicine that stopping smoking increases the expectation of life."

SHINE, K.I., University of California, Los Angeles

"Contractile calcium in cardiac muscle: Observations with nicotine and quinine." (876)

"Nicotine and quinine effects upon mechanical function and ^{45}Ca exchange were investigated in the isolated perfused rabbit interventricular septum. Nicotine transiently increased developed tension and dP/dt without changing resting tension. Reserpine administration decreased but did not abolish the inotropic response to nicotine and did not facilitate a change in resting tension. No contracture was induced by 20 mM nicotine during zero calcium perfusion.

"0.1-2.0 mM of quinine reversibly depressed tension while 5.0-20 mM induced a contracture reaching 60% of twitch tension in the presence of 1.5 mM Ca. 5-20 mM quinine induced a phasic contracture during zero calcium perfusion averaging 29.4±1.8% of twitch tension in blood perfusate and 22.5±3.4% in HEPES buffer. 200 uM lanthanum reduced this contracture to 14.3±3%, but did not prevent it nor did this concentration of lanthanum prevent contracture when calcium perfusion was resumed. No effect upon ^{45}Ca uptake or efflux could be demonstrated during exposure to nicotine or quinine.

"The contractile apparatus in rabbit ventricle was activated by 5-20 mM quinine but not by nicotine in the absence of extracellular calcium. This may result from release of a quinine sensitive intracellular pool of calcium."

HASS, G.M., SCOTT, R.A., McCLAIN, E.D. & HENSON, D.E., St. Luke's Medical Center, Chicago

"Inhibition of nicotine-induced calcific arteriosclerotic thromboarteritis in rabbits by adrenalectomy." (991)

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"Rabbits on specific regimens of dietary cholesterol, vitamin D or nicotine developed no peripheral arteriosclerosis. When these regimens were combined in a group of 48 rabbits, 27 developed calcific arteriosclerosis

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with thrombosis, 13 had arteriosclerosis without thrombosis and 8 had no arterial disease. The vasculo-toxic effects were not reproduced by the substitution of adrenalin for nicotine nor were they minimized by use of reserpine. Nineteen animals from which a sufficient amount of adrenal tissue had been removed did not develop peripheral arteriosclerosis or thrombosis. As a rule this required surgical removal of the left adrenal and cryogenic ablation of about two-thirds of the right adrenal with a residual after four months of not more than 250 mg of the regenerated right adrenal. Whether prevention of arteriosclerotic thrombosis was due to reduction of adrenal cortical or medullary function is not clear."

Central Society for Clinical Research and the Midwest Section, American Federation for Clinical Research, Chicago, November 2, 1972.

The following abstracts appeared in Clinical Research 20/4: October 1972 on the pages indicated.

SOLOMON, T.E., SOLOMON, N., SHANBOUR, L.L. & JACOBSON, E.D., University of Texas, Houston

"Direct effect of nicotine on exocrine pancreatic secretion." (p. 735)

"We have previously reported inhibition of pancreatic secretion of water and bicarbonate by nicotine in dogs and by cigarette smoking in man; this inhibition of intraduodenal neutralizers of gastric acid may be the link between cigarette smoking and duodenal ulcer disease. We investigated the mechanism of pancreatic inhibition by nicotine. An in vitro preparation of the rabbit pancreas was used in which the organ was suspended in Krebs solution and gassed with 95% O_2-5%CO_2. The main pancreatic duct was cannulated to collect spontaneously secreted juice comparable in amount and composition to in vivo secretion. Addition of nicotine (10 mM) to the bath for 1 hour caused highly significant reductions of 33±8.0% in volume, 13±2.1% in bicarbonate concentration, and 39±6.0% in bicarbonate output (values expressed as percent change between nicotine hour and preceding control hour; n=6; there was no significant difference between comparable hours in a separate control series of 4 experiments). In 6 anesthetized rabbits, smoking doses of nicotine (100 to 400 µg/kg-hr, i.v.) also inhibited spontaneous secretion: decreases of 23±6.3% in volume and 31±5.8% in bicarbonate output were seen (data presented as for in vitro above; all p values for in vitro and in vivo data less than 0.01). It appears that nicotine inhibits exocrine pancreatic secretion of water and bicarbonate by direct effect on cellular mechanisms."

FALK, L., DEINHARDT, F. & WOLFE, L., St. Luke's Medical Center, Chicago

"Transformation in vitro of nonhuman primate lymphocytes by Epstein-Barr virus." (p. 793)

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"Epstein-Barr virus (EBV), a herpes-type virus, causes infectious mononucleosis (IM) and has been implicated as the etiologic agent of Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC). Lymphocytes from IM patients and cells from BL and NPC frequently yield lymphoblastoid cell lines after cultivation and EBV is always associated with these cell lines.

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"Peripheral squirrel and marmoset lymphocytes (recipients) were transformed in vitro into lymphoid cell lines after cocultivation with lethally irradiated (6000 r), EBV-carrying human lymphoid cells (donor). The monkey lymphocytes became established as cell lines after 25-35 days of cultivation; donor and recipient lymphocytes, cultured separately, failed to form cell lines. Chromosomal analyses of the cell lines revealed normal diploid squirrel monkey and marmoset karyctypes. EBV antigens were demonstrated in the monkey cell lines by immunofluorescent staining. These results confirm and extend previous reports of transformation by EBV of lymphocytes from squirrel monkeys and marmosets (Miller et al. PNAS 69: 383, 1972) and gibbons (Henle, personal communication). Despite the proven susceptibility of marmosets to various oncogenic viruses, experimental infection with EBV has not succeeded, but attempted infection with EBV transformed autologous lymphocytes has not been investigated. The transformed lymphocytes have been inoculated into the autologous monkeys and their clinical and immunological responses were studied."

BROUN, G.O., Sr., SWEET, H.C., KINSELLA, P.W., SCHMIDT, R.R. & PUDER, B., St. Louis University, Missouri

"Factors affecting data on prevalence of pulmonary emphysema." (p. 805)

"Knowledge of past incidence of chronic obstructive pulmonary disease (COPD) is essential to establish the role of smoking, air pollution and respiratory infections in its epidemiology. The diagnostic terms, emphysema, chronic bronchitis and asthma are used irregularly and the true incidence of COPD is more closely reflected in combined data on these conditions. Recorded U.S. mortality attributed to emphysema increased markedly from 1950 to 1968. In the University Hospital a study of COPD began in 1947 and a pulmonary laboratory was established in 1950. A marked increase in admissions for COPD occurred after 1948, reaching a maximum in 1959. A treatment program involving reduction in smoking, use of bronchodilators, inhalation therapy, and treatment of respiratory infections was followed by a definite reduction in COPD admissions and mortality so that by 1969-1970 the level approaches that of 1949-1950. In other hospitals where no similar study program existed and where a pulmonary laboratory was established at a later date an increase in COPD admissions occurred after the laboratory became operative and a definite peak has not yet been reached. The date of onset of chronic cough in individuals later observed with COPD provides information not dependent on laboratory studies. It provides a rough estimate of the time when factors causing bronchial irritation became operative. Our data indicate that this occurred in the late 1940's and early 1950's. Only pulmonary function studies show the true incidence of COPD."

CANTRELL, E., MARTIN, R., WARR, G. & SHAW, C., M.D. Anderson Hospital, Houston

"Aryl-hydrocarbon hydroxylase induction in human alveolar macrophages." (p. 805)

"Aryl hydrocarbon hydroxylase (AHH) is an inducible membrane-bound microsomal enzyme found in many tissues throughout the body. Because

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cigarette smoke contains potential carcinogens such as 3-methylcholanthrene and benzpyrene, the degradation of these polycyclic hydrocarbons by lung cells is of particular importance. Levels of AHH were measured fluorometrically in pulmonary alveolar macrophages (PAMS) obtained by saline pulmonary lavage from healthy volunteers who were either smokers or nonsmokers. AHH levels were low in PAMS from 7 nonsmokers, with a mean (+SE) activity of .008 ± .003 units (1 unit = 1 picomole hydroxybenzpyrene/min/10^6 cells). PAMS from 6 healthy volunteers who regularly smoke from 10 to 20 cigarettes per day contained higher AHH levels with a mean level of .15 ± .04 units ($P < .001$). AHH induction was studied in PAMS from serial lavages performed on a healthy 29 yr. old male volunteer who had not smoked cigarettes for six years previously. AHH activity was .010 and .009 units in PAMS from 2 control lavages 4 months apart. One week after smoking resumed, the level of AHH rose slightly to 0.13 units. By 30 days, however, AHH activity had increased three-fold to .041 units. These studies indicate that AHH is inducible in vivo in PAMS by cigarette smoking. These actively phagocytic cells may serve as a first line of defense in the lungs to protect the body from potentially carcinogenic chemicals in cigarette smoke."

SWEET, H.C., BROUN, G.O., SR., KINSELLA, P.W. & PUDER, B., St. Louis University, Missouri

"Smoking as a factor in the development of emphysema." (p. 809)

"Many reports indicate that cigarette smoking is a major factor in the development of chronic obstructive pulmonary disease (COPD) the pathology and clinical history of which resembles the development of pneumoconiosis. To determine whether there is an increase of severity of COPD associated with progressively more cigarette smoking, the smoking history of 1200 patients who have had pulmonary function tests has been correlated with the severity of pulmonary function impairment. Smoking history was evaluated by pack years, i.e. one pack per day for one year equals one pack year.

"Nonsmokers show the least amount of impairment but 14% of the nonsmokers tested showed evidence of COPD.

"One out of five people who have smoked twenty pack years have severe COPD and over 50% of those who have smoked over forty pack years show moderate to severe emphysematous change.

"A marked increase in cigarette consumption in the U.S.A. began in 1941. In 1600 cases of COPD the time of onset of chronic cough was recorded. Cases with chronic cough increase strikingly after 1943 and the two curves closely parallel one another for more than 10 years.

"Tobacco, however, can not be the only factor in the development of COPD since there is a small but significant group of nonsmokers who develop the disease and some individuals maintain normal pulmonary function even after more than forty pack years of smoking."

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Annual Clinical Congress, American College of Surgeons, San Francisco, October 1972

The following news report appeared in Medical Tribune 13/42: 1, November 1, 1972.

FRALEY, E.F., ELLIOT, A.Y., HAKALA, T.R., CASTRO, A.E. & CLEVELAND, P., University of Minnesota

"Human cancers: An RNA virus held isolated."

"A propagatable RNA virus has been isolated directly from a series of human cancers.

"Dr. Elwin E. Fraley, chief of the division of urology at the University of Minnesota Medical School, reported to the American College of Surgeons here that the virus, tentatively named EFMU-1, was found in the surgical specimens or primary tumor cell cultures of four successive adult male patients with tumors of the urothelium who were extensively studied....

"While not yet ready to term the virus oncogenic, Dr. Fraley noted that 'this virus very closely resembles viruses that are known to produce cancers in animals....'

"Dr. Fraley refused to comment about any attempts to test infectivity of the virus in animals.

"All four patients with the transitional cell tumor, found in the lining of the renal pelvis, and the virus had antibodies to that virus. Antibody formation was not seen in age-matched controls of 12 patients without cancer or some 20 patients with other types of tumors....

"At best, oncogenicity of the EFMU-1 virus in man, Dr. Fraley observed, can be shown only indirectly. Since it is an RNA virus, 'it theoretically should be susceptible to chemotherapy' of the sort that affects other RNA viruses. Viral etiology, he said, will be proved when 'the virus is eliminated by chemotherapy and the course of the disease is altered.'"

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16. ERRATA

CD November 1972: - The senior author of the abstract on page 9 should read "OBERMAN, A." The author listed as "CHRISTOPHER, J." on page 34 should read "CASTON, J.C."

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